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FUNDAMENTAL CONCEPTS DETERMINING A PHILOSOPHY OF TREATMENT IN MAMMARY CARCINOMA*

A Review

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IN THE FIRST HALF of the present century, undoubtedly the golden era of surgical practice, a radical excision of the primary neoplasm has been the cornerstone on which attempts at success in the therapy of carcinomatous lesions generally have been founded. Further success with this therapeutic programme has been sought by directing attention to earlier diagnosis in order to forestall the development of distant metastases, and by increasing the extent of the operation in order to encompass the neoplasm and its local nodal metastases more completely. With increasing technical skill, both surgical and anæsthetic, and more intelligent attention to blood, fluid, electrolyte and metabolic requirements, it is undoubtedly true that it is now possible to contemplate with surgical aplomb any degree of excisional therapy considered necessary in these lights, provided certain vital organs are not hopelessly prejudiced in the process. Whether or not sufficient benefit, either physical or mental, results when one takes advantage of these possibilities to recompense the patient for the increasing hazards of postoperative mortality and morbidity to which he is subjected, is a problem requiring careful assessment indeed by a surgeon blessed with mature judgment rather than by an enthusiastic technician.

When one assesses the results obtained in breast cancer by attention to these considerations it seems amazing, and not a little ludicrous, that their potential efficiency has not been challenged until recently. Because this cancer is the commonest malignancy affecting white women[1] a tremendous mass of data is available from which pertinent analyses and interpretations may be made. Because too the lesion lies in an accessible organ earlier diagnosis should be within the bounds of clinical possibility and, because in addition the organ involved is not vital to health, radical surgical methods may be undertaken for the wide removal of the malignant process and the organ in which it has arisen. Finally, it is technically possible to remove the local lymph nodes either by standardized axillary dissection or by super-radical procedures including the supraclavicular and internal mammary chains as well. Breast cancer then fills all the requirements thought necessary for ideal cancer surgery possibly more acceptably than any other malignant lesion, and yet the survival rates as judged at the five-year interval show a tragically disappointing improvement when compared to similar periods of survival in untreated patients. In the latter group a rate of 20 to 22% certainly compares favourably with that of approximately 30% in those treated, especially as many unfavourable or hopeless cases are excluded from consideration in reports of results of treatment in selected series.

Clearly a critical appraisal of these results demands an intelligent reassessment of the problem of therapy in mammary carcinoma. Professor McKinnon,[2, 3] long voicing doubts as to the efficacy of surgical treatment, has for several years stressed the need for this clinical awakening to the actual statistical facts, basing his warnings on the lack of evidence of any significant decline in the mortality rates for breast cancer in Canada. Such a decline would, of course, be apparent were the treatment of this lesion indeed effective in curing an appreciable number of patients. In previous publications,[4, 5] it has been suggested that improvements in diagnosis and factual errors in death certification might explain in part this failure to influence the

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death rates, but with the inexorable passage of the years one cannot fail to accept the fact that these statistics do not lie nor are they misleading. As confirmatory evidence, Phillips and Owchar,[6] Canadian Cancer Society statisticians, have recently reported results of a 13-year survey in which again no significant fall in death rate was discovered over the period analyzed. It is interesting to note that a slight trend towards improvement is apparent in these figures. If continued at its present rate for another 10 years this improvement would then become statistically significant. Whether this would necessarily represent the results of treatment or of other factors as yet unrecognized, is impossible to predict.

At any rate, it is obviously true that patients are not cured by an apparently satisfactory operation because spread has occurred beyond the range of the excision before operation. This observation focuses attention once again on a conundrum long puzzling to surgeons: patients with a large primary lesion and a prolonged clinical history of disease may do well with treatment, or occasionally even without any treatment whatsoever, whereas the intelligent but unfortunate patient who recognizes a small lesion and reports it promptly may, despite early attention, succumb very rapidly to her disease. One must assume that the die is cast long before the pathological change is recognized and that the eventual outcome depends primarily on the nature of the neoplasm rather than on the type of treatment advised. Whether or not a favourable result is obtained by treatment reflects the relative weighting of the interplay between the host and the tumour in the preoperative period—a situation about which no exact pathological or physiological knowledge is as yet available. Despite our vague and indistinct appreciation of these obscure factors we must have some means of representing this appreciation in order to incorporate this incomplete knowledge into an intelligent approach to the problem.

With this necessity in mind it is perhaps easiest to consider the host and the tumour as two individuals in competition for survival. Concepts designed to describe this competitive activity are presented in Figs. 1 to 6.

In the first place (Fig. 1) the host attempts to prevent extension of the tumour by creating a barrier of fibrous tissue to imprison the malig-

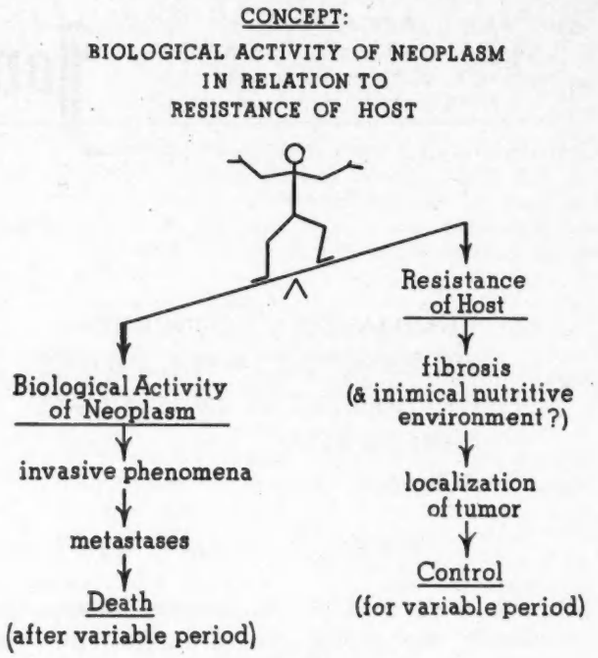

Fig. 1

nant cells and by its contraction cut off or impoverish their vital blood supply. The neoplasm attempts to escape this imprisonment by active invasion and destruction of tissues with which it comes in contact during proliferative growth, in this way spreading to distant sites if lymphatic or hæmatogenous channels are entered. The clinical evidences of these two fundamental processes, summarized in Table I, form a convenient basis for the classification of breast disease. I have previously described such a modification of the Richards classification[5] in an attempt to appreciate these most significant attributes of the primary neoplasm. The competitive activity is, of course, not as simple as that implied by a consideration of two such clear-cut pathological processes, and is probably represented more basically by the cellular demands for substances essential for adequate nutrition on a vital physiological level (Figs. 2, 3). If the host cells are capable of continuing to garner these substances in sufficient amount for normal function, the patient's general health will be unimpaired and a minimum of such material will remain available for the tumour cells, which consequently cannot proliferate rapidly. If, on the other hand, the tumour cells are so active and have such vitality that they utilize the majority of the essential metabolic requirements for cellular growth, the neoplasm will flourish and be capable of rapid growth, invasive activity, and dissemination; whereas the

TABLE I.

CLINICAL EVIDENCES OF MALIGNANT NEOPLASIA IN BREAST LESIONS

↓

THE RESULT OF COMPETITIVE ACTIVITY
BETWEEN
TWO FUNDAMENTAL ATTRIBUTES OF HOST AND NEOPLASM

Reaction of the host to presence of neoplastic cells ↓ *retraction phenomena*			*Biological (or invasive) potentiality of the neoplasm* ↓ *invasion phenomena*		
Skin	*Nipple*	*Deeper structures*	*Skin*	*Nipple*	*Deeper structures*
Dimpling	—Retraction (inversion) —Deviation	Attachment of tumour to underlying structures (limitation of mobility)	Ulceration	Superficial ulceration (Paget's disease)	Fixation of tumour to chest wall structures (Tumour becomes immobile)

Signs due to reactionary fibrosis producing protective scar tissue barrier to tumour extension	*Additional signs of vascular involvement*	
	Lymphatic invasion	*Blood stream invasion*
	Permeation— peau d'orange satellite nodules Embolism— nodal metastases	Embolism— distant metastases —pulmonary —osseous—vertebral column

↓ *Control (for variable period)*

↓ *Death (after variable period)*

host cells, deprived of their nutritive needs, lose their ability to proliferate, with eventual wasting of the patient's tissues and also failure of effective host resistance, leading progressively to cachexia and death. The cachectic state may also result from inadequate function in vital organs, such as the bone marrow and the liver, partially destroyed by the malignant process. At any rate, attempts to influence this vital competition between the biological activity of the tumour and the resistance of the host represent one of the most fruitful and logical fields of cancer research from which much may be hoped in the future. The anti-tumour effect of inanition resulting from limiting calorigenic intake is but one experimental observation supporting this thesis that vital metabolic requirements must be met if the tumour is to flourish[7].

It has been stated in some quarters[8] that hæmatogenous dissemination occurs before diagnosis is made in active or invasive tumours, and that, at least in this group, early diagnosis is ineffective in improving the cure rate resulting from local therapy. At the other end of the scale, McKinnon[3] has expressed the opinion that very inactive lesions having the pathological appearance of carcinoma may in fact be non-lethal neoplasms incapable at any time of setting up metastases; consequently he doubts whether the high survival rate in Stage I cases necessarily indicates the value of early treatment, for the assumption that all would eventually produce metastases is not proven. Nonetheless, it is generally accepted that mutation from a local pathological change in the cell to a cell capable of destruction and invasion will eventually take place, a contention supported by the frequent clinical observation of recurrence locally or in metastatic sites 10, 20 or even 30 years after removal of the primary neoplasm. Certainly it seems reasonable to assume that all gradations

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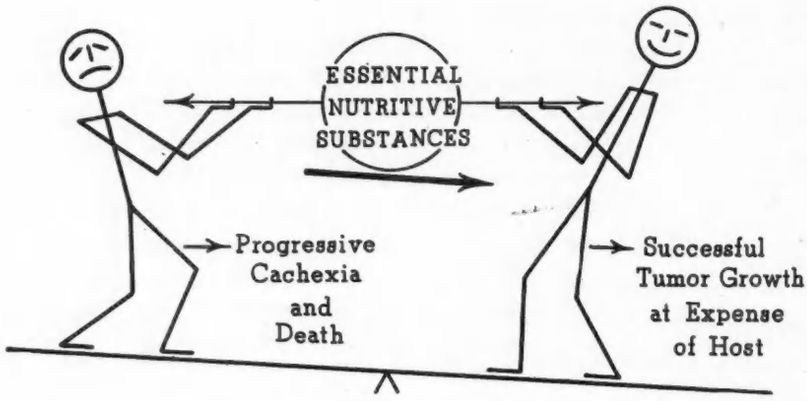
CONCEPT:

HOST VERSUS TUMOR COMPETITION



wasting of host tissue if unsuccessful in the competition for essential metabolic requirements

proliferation of tumor tissue if successful in the competition for essential metabolic requirements

Fig. 2

occur between these two extremes of the disease, although unfortunately the relative frequency is undoubtedly weighted heavily towards the biologically active and invasive neoplasm, in which case cure may be impossible. Attempts to determine whether this potentiality exists preoperatively in those patients in whom metastases are not apparent clinically are a logical outcome of this speculation. As yet, no method of practical application has been designed, although anterior chamber transplantation to laboratory animals, a possibility assessed by Greene[9] and found to be associated with the ability of the tumour to metastasize, is an attractive concept inviting further clinical trials.

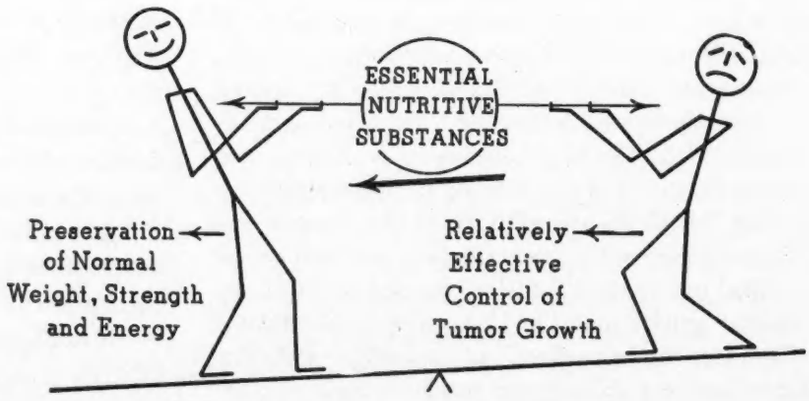
With these fundamental considerations in mind, the problem then becomes one of developing a plan of therapy for patients with localized primary disease and one for those with metastatic disease either detectable at the time of the original examination or appearing in the postoperative period.

A. TREATMENT OF THE PRIMARY LESION

If one accepts the theory that gradations exist both in the activity of the neoplasm and the resistance of the host, and also that invasion will eventually take place, the length of time the pathological lesion has been present becomes an important consideration in determining the extent of the disease locally and at distant sites. In the group, admittedly small in number, in whom tumour growth is biologically inactive and in whom host resistance is high—a combination resulting in prolonged localization of the lesion—early diagnosis and treatment may then be expected to give the best chance of permanent cure. It seems quite reasonable to assume that the growth of any cancer occurs in three stages: firstly, a local extension into the adjacent tissues; secondly, permeation of tissue spaces and thence lymphatic channels from which embolic phenomena can develop; and, finally, invasion through the barrier of the blood vessel walls

CONCEPT:

HOST VERSUS TUMOR COMPETITION



host able to maintain normal bodily function as long as it competes successfully for essential metabolic requirements

tumor unable to grow effectively if the host utilises the majority of the available essential nutritive factors

Fig. 3

to reach venous radicles from which hæmatogenous metastases may develop. In this thesis one would expect that the lesion, in favourable cases, may be at one stage confined to the breast, at a later period restricted to the breast and the nodal areas, and finally associated with distant metastases of hæmatogenous type. However, it is essential to realize that one is talking about microscopic changes in these three stages of progression, and it is at once apparent that a tumour which becomes palpable only when it has reached a size of about 1 to 2 cm. in diameter is at that stage a very gross lesion indeed as far as its microscopic picture is concerned, and may already have invaded blood vessel channels and produced extension to distant organs which cannot be affected by any local therapy. Whether or not this hæmatogenous dissemination always occurs before clinical diagnosis is possible represents the fundamental problem in attempting to determine whether cure can ever be obtained in this disease by local treatment. The fact that all reported series contain cases in which long-term survivals of more than 10 years have been produced even in the face of metastatic axillary nodal involvement (an attribute taken to indicate the potential malignancy or metastasizing capability of the lesion) suggests that this general dissemination does not necessarily occur in every case. The validity of this conception of the disease is supported by observations[10] indicating that a clinical staging of the type described above is still the best means available on which to judge the prognosis in any patient, a marked correlation being apparent between the stage of the disease and the five-year survival. Therefore, it is felt that surgical treatment of the primary lesion when unassociated with clinically detectable hæmatogenous metastases is a worthwhile and intelligent method of attack upon the disease in the hope of effecting a cure in a small proportion of the patients.

Admittedly, one can cure only those patients capable of being cured because of the inherent nature of their disease, but the removal of the obvious primary lesion carries with it other implications which cannot be overlooked and will in the majority of cases be just as important to the patient as the cures effected in favourable cases. In the first place, there can be no doubt that the time has come when, in view of our present knowledge of cancer and its biological capabilities, less emphasis should be placed upon the desperate and often frenetic search for new surgical procedures in an unreasoning grasp for the magic of "cure", and more attention paid to the palliative effect of the treatment programme upon the patient's physical and mental suffering. Certainly there can be no argument with the observation that a patient who, coming to her physician with a lump in the breast, is subsequently relieved of the obvious clinical evidences of the disease, considers herself cured, and no one would care to disabuse her of this conception of her disease. Despite the fact that she may develop recurrences after a period of freedom from complaints, which may often last for several years, the personal benefit of this treatment cannot be overemphasized. Then again, the clinical impression that length of life is prolonged by treatment of the disease process, whether in primary or metastatic sites, has statistical support,[11, 12] and surely this is a boon for the patient whether its significance is appreciated or not. These benefits of treatment are in accord with true Hippocratic precept, but one must also recall that relief of suffering is but one facet of medical service as revealed in this oath. The pertinent paragraph states, "I will carry out that regimen which according to my power and discernment shall be for the benefit of the sick and will keep them from harm and wrong." In the light of modern technical possibilities, how far-sighted indeed was this statement of principle and how carefully do we have to attend to the principle when determining the type of surgical treatment indicated.

In choosing the surgical procedure, many possibilities are available. All must be assessed with the realization that local treatment is sensible only on two bases: firstly, to cure localized cancer, and, secondly, to provide physical and mental relief, even in patients in whom survival will be prolonged but for a relatively short time. The treatment must therefore be designed to eradicate the local disease, prevent its local recurrence, and possibly diminish the danger of early dissemination from adjacent disease not eradicated by the operation. Standard radical mastectomy has been criticized on two scores in these regards. On the one hand, it has been said to be too radical because if the axilla is uninvolved it is unnecessary; and if the axilla is involved, it may actually produce, by the operative manipulation, dissemination of disease

beyond the zone of surgical excision. On the other hand, it has been stated that it is not radical enough because it makes no attempt to excise the lesions which we now realize are frequently present in the supraclavicular triangle and, possibly more important still, in the internal mammary chain. Certainly in medial quadrant lesions one would be hard put to ascribe any rational basis for a dissection of the axilla without attention to the internal mammary chain; whereas in upper outer quadrant lesions the infrequency of this mediastinal involvement in favourable lesions may allow us the luxury of belief in the value of axillary dissection, in view of the percentage of long-term survivals almost universally noted in such Stage II lesions.

In discussing simpler forms of mastectomy,[3] one must point out that it is extremely difficult clinically to assess correctly the degree of axillary involvement; simple mastectomy with early unrecognized axillary involvement may ignore a group of these patients in whom a five-year salvage rate of at least 30% is constantly reported. Viable cells will persist in an appreciable number of these cases after postoperative irradiation of the axilla, and one cannot be certain when these cells will be capable of invasion through the barrier of reactive fibrous tissue to produce recurrent or disseminated disease. With the limited dissection local recurrences are admittedly more frequent; and one is not certain, if the precept of a complete simple mastectomy is always followed, whether in fact a partial dissection of the lowermost axillary nodes is not carried out in addition to the mastectomy, with the very dangers of an axillary dissection advanced by the opponents of a radical mastectomy. The major objection to the routine acceptance of simple mastectomy, however, depends on the fact that it is considered a simple procedure, and as such will be performed by surgeons lacking in the skill and training essential for the performance of a radical mastectomy. Inadequate procedures will inevitably be the result, with an associated tendency to inadequacy of postoperative radiation therapy, which even in its most effective application cannot compensate for incomplete excision of the lesion and the breast tissue. When properly performed, there can be no doubt that the results of a complete simple mastectomy followed by expertly administered radiation therapy in cancericidal dosage approximate those obtained by radical mastectomy, without the development as frequently of the complications of shoulder stiffness and arm swelling. Hence one cannot fail to appreciate this procedure, which may well be that of choice in selected cases provided it is performed in strict accordance with the original principles enumerated above. Nonetheless, it is fascinating to consider that it is a procedure proven of value, although quite possibly conceived on false premises. Originally designed to forestall delay in wound healing, thus allowing early postoperative radiotherapy, and also to avoid the theoretical hazard of axillary dissection in the presence of disease, it would seem much more probable in the light of present concepts that its effectiveness demonstrates once again that the results of any treatment are determined primarily by the nature of the disease rather than the treatment to which it is subjected.

As regards more radical surgical procedures, one must be certain that the benefits accruing to the patient will compensate for the increased suffering (as represented by the postoperative mortality and morbidity) which inevitably follows these more extensive surgical procedures. It will be many years, unfortunately, before it is possible to assess accurately the results of the superradical operations; but in view of the fact that the majority of patients will have hæmatogenous metastases at the time the surgical procedure is performed, one cannot but feel that we are taking advantage of the possibility that such procedures can be carried out with the aid of modern technical measures without any real hope that a proportional benefit will result for the patient. Possibly simple block dissection of the internal mammary chain in medial quadrant and subareolar lesions may find its place in the treatment programme eventually chosen.[14]

In other centres radiation therapy has been combined with the standard radical surgical treatment. There can be no doubt that in the attack upon disease which is still localized, this combination has definite potential advantages. Particularly if it is used preoperatively, there are the theoretical possibilities that it may diminish the biological activity of the neoplasm and also increase the local tissue resistance of the host by increasing the production of fibrous tissue. In subsequent dissection the fact that perilymphatic fibrosis will have produced an appreciable degree of lymphatic obstruction also represents

a theoretical advantage which makes it possible for the surgeon to contemplate axillary dissection without worrying too much about the danger of disseminating disease. It would appear that such additional procedures will be most valuable in the patient with locally advanced disease and a prolonged history without any evidence of hæmatogenous metastases, thus suggesting a slowly metastasizing lesion. This group of patients is very similar to that described by Macdonald,[15, 16] who stresses the fact that natural selection of this kind is the best indication of operability, and possibly resectability, in human cancer, and that curability increases with the duration of symptoms in resectable cases. Obviously, a lesion which remains apparently localized after a lengthy history, despite the extent of its local growth, represents one of low biological activity and delayed metastasizing potential; therefore it is one which will repay the most radical possible combination of local excision and cancericidal radiotherapy, preferably delivered as described previously in preoperative dosage. The results obtained in this manner[4] when dealing with these locally advanced lesions would seem to support this contention not only by an improved survival rate but also because local recurrences, surely the best method of assessing the results of treatment of a local disease, are encountered no more frequently than in more favourable lesions of earlier stage.

With so many conflicting opinions and therapeutic plans it is difficult, if not impossible, to outline any programme which will not be open to vigorous criticism on one score or another. Actually, changes are almost certain in such a programme as our knowledge increases and critical appraisal of its effectiveness is made as time passes. With the fundamental problems considered above in mind, however, some reasonable suggestions may be made.

One Regimen of Therapy in Primary Mammary Carcinoma

When considering prognosis and results of treatment, it has been our custom in the past to use as a reference basis the five-stage classification which utilizes signs demonstrating the invasive nature of the carcinoma and the resistance of the host as determining factors, and to which previous allusion has been made. In planning a treatment programme, a simplification of this classification has been suggested in which the first two stages are grouped together again, and stages III and IV also considered as a unit representing locally advanced disease. The fifth or final stage remains a separate problem to be discussed subsequently when the management of those unfortunate patients with clinically detectable metastatic disease is considered.

A. *Stages I and II.*—Because it is so difficult to assess correctly on clinical grounds the presence or absence of pathological involvement in the axilla (and because the actual surgical plan can only be determined on the basis of a preoperative opinion), these two stages are grouped together and treated identically as far as excisional therapy is concerned. With outer quadrant involvement in which metastases to the internal mammary chain are relatively infrequent a radical mastectomy is advised. If, however, the lesion is medially situated, having consequently a much higher incidence of mediastinal spread, one might reasonably question the rationale of employing the standard radical procedure and view favourably some such attack on the internal mammary chain as the Urban procedure. Nonetheless, because it has not yet been proven that the benefit resulting from this extension of the surgical attack is sufficient to permit unquestioning acceptance of the resultant increase in postoperative morbidity, and because involvement of the mammary chain is not inevitable, particularly in a patient with a lesion of this early local stage, we still prefer the standard radical dissection. Actually the technical considerations of this super-radical procedure make it one that can be safely performed only in larger institutions. The most reasonable alternative to the standard procedure we believe to be a simple mastectomy followed by postoperative irradiation of the nodal areas. On the other hand the axillary dissection, if proven negative, might be considered as having the advantage of avoiding the necessity for irradiation of the axilla, thus allowing one to confine irradiation to the mediastinum alone when the lesion lies in the medial part of the breast. If, on the other hand, the axilla proves to be involved, we believe it to be more adequately cleared by operation followed by radiotherapy than by radiotherapy alone.

Regardless of the surgical procedure chosen, if evidence of nodal metastases is discovered on

pathological examination, radiotherapy should be directed at all three nodal areas in view of the free communication that exists among all components of this encircling chain of drainage nodes. Clearly, in all medial quadrant and subareolar lesions a separate mediastinal port is now indicated.

It should be mentioned that a complete radical dissection of the axilla is quite feasible without removing the pectoral muscles, and some may prefer this method if worried about the additional surgical insult of muscle excision in a poor-risk patient or fearful of limitation of function postoperatively with stiffness of the shoulder or swelling of the arm. Both of these latter complications will be lessened appreciably by this modification of the operative procedure. Admittedly, the fascial plexus of lymphatic channels is not removed even though potentially the site of extensive neoplastic permeation, but despite this theoretical consideration local wound recurrences do not appear to be encountered more frequently in these early lesions. With this possibility in mind, however, some may feel that postoperative irradiation will always be indicated, at least to the chest wall, although it is not our custom to advise its use routinely. We have found this procedure to be quite simple technically, with adequate exposure of the entire axilla provided the arm is placed in a position which relaxes the pectoralis major muscle so that the latter may be fully retracted, the coracoid attachment of the pectoralis minor being divided to aid the exposure. It is interesting to discover that George Crile, Sr., during his entire surgical career covering the very decades in which radical mastectomy remained unchallenged, resolutely refused to remove the pectoral muscles, and his successors are now able to report[17] that his survival rates were comparable in every way to those of others in the same Centre who stressed the necessity for muscle excision.

B. *Stages III and IV.*—In those cases of more advanced local breast disease demonstrating retraction or invasion phenomena, particularly if a long clinical history is obtained, one may be hopeful of dealing with a patient selected by natural processes as suitable for therapy, harbouring as she does a neoplasm potentially of local biological activity and one to which she has shown an effective resistance. Because then the disease may still be localized, in which event local recurrence will be the main problem, a radical local attack is indicated, being best accomplished we believe by combining cancerocidal preoperative radiotherapy with subsequent radical mastectomy as previously reported.[4, 5] With a rapidly growing lesion of this type, particularly if already of Stage IV degree when clinically recognized, one would be less enthusiastic about the extensive surgical dissection, but the importance of preoperative radiotherapy here too cannot be over-emphasized, regardless of the operation—if any—to be subsequently employed. One can be almost certain that an operative attack without the protection of local radiotherapy beforehand is doomed to failure and open to the hazard of early—and often almost immediate—local recurrence, occasionally progressing rapidly to a tragic cancer en cuirasse. The modified radical mastectomy described above may be considered preferable here also, but all involved muscles must, of course, be always excised. For the same reasons outlined above, a simple mastectomy would be the most acceptable alternative, with the proviso that radiotherapy should be preoperative rather than postoperative in an attempt to limit the incidence of local recurrence as much as possible.

C. *Stage V.*—When distant metastases are present, treatment of the local lesion is purely palliative although it has definite physical as well as psychological value, particularly when an extensive local lesion, possibly complicated by ulceration and secondary infection, is producing general effects upon the patient's metabolic state. In these cases simple mastectomy is usually considered the method of choice, with local radiotherapy preoperatively dependent upon the extent of the local lesion.

B. TREATMENT OF METASTATIC DISEASE

Once it becomes apparent that breast cancer has spread beyond the limits of the breast and axilla, it is no longer possible to plan on attempting curative therapy. Therefore, one must not concentrate on treatment of the local lesion alone but must view any therapy of the primary disease or the metastatic sites in the broader light of its effect on the patient as a person. Palliation now in truth becomes the basis for successful treatment, and the overbearing consideration in any form of therapy is the effective relief of suffering and prolongation of life it may be expected to

afford. The method used must not produce discomfort or distress incommensurate with the benefit obtained, and prolongation of life must be of sufficient length to make it worthwhile and afford a reasonable expectation that it may be led in comparative freedom from discomfort, with relatively normal functional activity. Creating an invalid who merely "endures" a momentary reprise may in fact be condemned as harmful therapy and contrary to true Hippocratic precept, for the patient neither wishes nor appreciates such a useless survival. On the other hand, effective relief of a distressing symptom associated with an increase in the survival period, during which the relief may be truly enjoyed by one now able to conscientiously reap the harvest of her life with personal profit and at peace with her religious beliefs, is a boon not to be denied any who are acceptable candidates for such treatment.

Although reports of the results obtained in the management of metastatic disease are infrequent, there is no doubt that much that is rewarding may be accomplished by established methods of treatment. Certain pertinent data will bear repeating, and Peters has prepared a very painstaking report[12] of such data which is supported by recent observations at the University of California.[18] The most frequent sites of initial recurrence are the skin of the chest wall (local recurrences), bone (particularly vertebral column) and lung. The first two of these sites fortunately are peculiarly susceptible to radiation therapy; after irradiation of localized recurrences in these areas, there was an expected prolongation of life of more than one year as compared with a group of untreated patients (24 months' survival versus eight months'). As might be expected, metastases occurring later than one year after operation have a better prognosis with respect to length of survival, due probably to the fact that the metastatic lesion has low biological potential and therefore responds favourably to any inimical factor in its environment. Shimkin *et al.*[18] have also demonstrated that the time after operation at which recurrences become clinically manifest is influenced by the stage of the disease at the time of initial operation, and that the length of life after recurrence is influenced significantly by the type of recurrence; it is most prolonged in local recurrences or osseous metastases, the very lesions found above to respond so well to radiation therapy. With these results in mind, one would not hesitate to advise such treatment in these types of recurrent disease, as most worthwhile palliation may be reasonably anticipated. The healing of ulcerating skin recurrences and the disappearance of local nodules or lymph node metastases have tremendous psychological implications for the patient; and the relief of pain, which may be dramatic and is indeed often associated with radiological evidences of calcification in the osteolytic metastases of skeletal involvement, has to be seen to be fully appreciated. When such relief coincides with prolongation of survival time, the value cannot be overemphasized.

When susceptible metastases or recurrences fail to respond to further radiotherapy; when metastases become too widespread to permit effective irradiation of the entire area of involvement; when the patient's tolerance to further treatment is exhausted as demonstrated by a falling platelet count, anæmia, or agranulocytosis; or when the disease affects tissues which cannot be irradiated safely, as in vital organs such as the lungs, or effectively as in visceral disease affecting inaccessible sites, one must look for other methods of management.

Radiation therapy with radioactive isotopes can be utilized effectively in two additional sites inaccessible to an external source. In both pleural and peritoneal involvement with extensive effusions requiring frequent aspirations for the relief of disabling symptoms, the instillation of radioactive colloidal gold has pronounced palliative effect, a favourable response being obtained in between one-half and two-thirds of cases.[19, 20] Particularly in patients having extensive pleural effusions is the necessity for frequent aspiration overcome, for in many of these patients no further aspiration need be performed after administering approximately 80 to 100 microcuries. Although this therapy is not designed to prolong life (the metastases being also widespread in most instances), it has such dramatic effect in this specific local area that one must consider it worthwhile palliation.

When no further methods of effective local treatment are available, the disease must in this event be attacked through the blood stream, either by adding something to the blood which is inimical to the continued growth of the tumour or by subtracting something from its vascular

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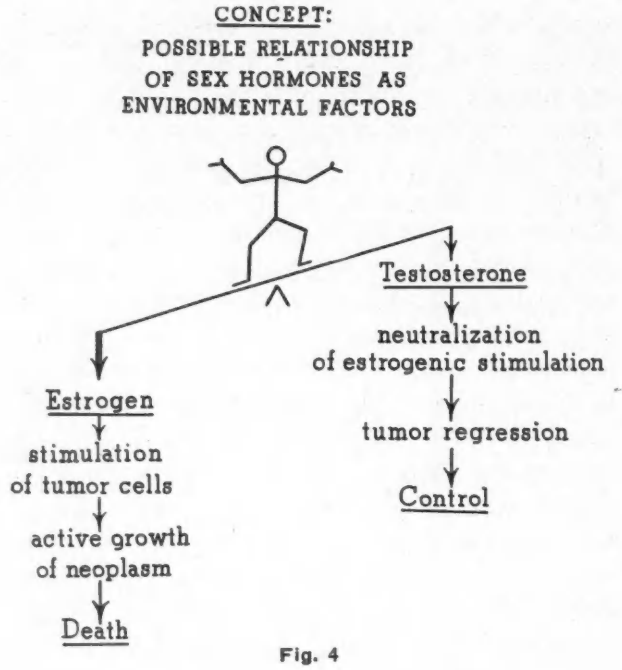

Fig. 4

supply which is essential for the sustenance of the neoplastic cell. For practical purposes the principle of this form of treatment is an attempt to create an unfavourable environment in which the malignant tissue finds it impossible to flourish. Once again concepts of practical value, although admittedly incomplete in exact physiological fact, are utilized to guide the surgeon in his attempt to carry out further treatment intelligently. These concepts will need further adjustments as our knowledge widens, but they present a working basis for the following hypothesis.

In the first place information has accumulated over the years, both of an experimental and a clinical nature, that the female œstrogenic hormone at least creates a favourable environment whether or not it is actually a carcinogenic agent itself. Therefore, it would appear reasonable to attempt to affect the metastases by altering the hormonal environment as far as the œstrogenic element is concerned. This balance, as diagrammatically represented in Fig. 4, can be tilted towards the androgenic side by the exhibition of testosterone or by the withdrawal of œstrogen, and information is now available concerning the effect of both these methods of management. Testosterone in adequate dosage (preferably at least 300 mg. weekly over a test period of 6 to 10 weeks) according to Peters[12] will be associated with subjective improvement in strength and energy and symptomatic relief in about 50% of patients treated, with objective evidence of a favourable response in about 20%. Approximately one-third of these patients survive longer than one year, representing a gain in life expectancy of some five months. These results would appear to be worthwhile, particularly in pulmonary metastases for which no known therapy was previously available, and in osseous metastases and local recurrences not suitable for further radiotherapy.

The exact mode of action of testosterone remains obscure because in a few cases the disease is undoubtedly accelerated both objectively and subjectively by its use, and in addition there is no doubt that therapy with œstrogenic preparations may also produce remissions in the disease process, particularly in postmenopausal women. This suggests that an ideal androgen-œstrogen balance may be essential for tumour growth, and tilting the balance in either direction may adversely affect the neoplastic cells, at least until they readjust to the altered environment in which they have to exist. In the experimental animal exact attention to optimum dosage of the œstrogen administered is necessary to produce mammary carcinoma, and smaller or larger doses are ineffective, possibly because of failure to create a suitable environment in which carcinogenesis may occur. On the other hand, as we shall see later, the larger doses may in fact deter the inception or growth of malignant cells by producing pituitary depression. Testosterone too may produce its effect as a result of similar pituitary depression or possibly by the stimulation of protein anabolism and physiological osteoblastic processes, having thus a general rather than a specific effect, aiding in the natural processes of host resistance by favouring the host cell in its competition for vital metabolic requirements. It is unlikely that testosterone is in fact primarily an anti-œstrogen, for the Memorial Hospital group have shown it to be ineffective in preventing the osteolytic effect of œstrogen when both are administered simultaneously to patients with osseous metastases.[21] Confirmation of this thesis is apparent in our observations that irradiation castration has not increased the response to testosterone nor has the previous response to testosterone proven of any prognostic value in predicting the results of œstrogen deprivation therapy.

It is a seeming paradox that therapy with œstrogenic substances may produce remissions

of subjective and objective type in metastatic disease, particularly of soft tissue lesions in postmenopausal women. Presumably this occurs through an upset in the existing and favourable androgen-œstrogen balance, or else by the pituitary depression attendant upon œstrogen administration in pharmacological dosage (15 mg. daily). At any rate, significant responses are reported in the postmenopausal group with objective remissions in about one-third of the patients for a satisfactory length of time (mean duration over one year).[22] It should be stressed, as might be expected, that exacerbations will occur with this form of treatment frequently enough in young women to make its use in this group unwise, and occasionally in the older group where the lesion is still œstrogen-sensitive. Particularly is this dangerous in those with osseous or hepatic metastases where activation may be associated with hypercalcæmia to critical levels if hepatic metabolism of the administered œstrogen is delayed. Therefore, one must always be on guard when supervising this form of hormonal treatment regardless of the age of the patient. An additional disadvantage is at once apparent when one finds that many patients can not tolerate œstrogen administration for an effective period without developing extreme nausea or vaginal bleeding.[12]

The importance of a favourable androgen-œstrogen balance, or at least of a hormonal environment to which the neoplastic cells have become acclimatized, is well represented by the frequently reported clinical observation that, with both types of hormonal therapy, a cycle of regression and reactivation may occur followed by a further regression when the hormonal therapy is discontinued. Similarly, it is occasionally noted that alternating from one hormone to the other may appreciably prolong the effectiveness of this type of treatment.

Definitive œstrogen deprivation may be brought about in several different ways: by radiological or surgical castration and by castration combined with adrenalectomy. One cannot discuss castration in the treatment of metastatic disease without considering its elective use in the treatment of primary mammary carcinoma. Horsley,[23] long a proponent of its performance coincidentally with the original mastectomy, now urges its routine use in premenopausal and menopausal women, basing his advice on improvement in over-all survival rates as compared with those in non-castrated patients. Because of the very definite menopausal dip frequently reported in survival statistics[24] it is at least reasonable to consider its use in the case of women between the ages of 40 and 50, for at a later age it is theoretically unlikely to be as effective if ovarian function is still further diminished by the time subsequent metastatic spread becomes apparent. However, no definite proof of this supposition is available, particularly in view of the fact that metastases, if they do develop, tend to appear very rapidly in this unfortunate group of patients. Actually we have discontinued an incipient plan of advising routine castration in these patients (originally suggested in view of the menopausal dip that was so apparent in our series of advanced cases having preoperative radiation[5]), because a complete study of 855 cases seen between 1937 and 1949[10] failed to show any appreciable relationship between age at onset of disease and survival rate. Perhaps in the locally advanced lesions it might still be worthwhile therapy, for the hormonal readjustments coincidental with the menopause may be sufficient to activate the impending mutation of these biologically inactive neoplasms into actively invasive tumours capable of widespread and rapidly lethal dissemination. In younger women, however, because their survival rate approximates that of the postmenopausal group, castration is not performed, for it is not thought to add to the patient's safety, and in addition it has been found, admittedly to our surprise, that subsequent pregnancy does not decrease the survival rates if the primary disease has been controlled.[12] Harrington[25] has also pointed out that it is possible for patients to bear children after radical amputation of the breast and to live for many years without recurrence. Therefore, to deny such a patient the privilege of maternity does not seem warranted provided a reasonable period of delay, probably at least a year, is advised in order to make certain that recurrent disease is not going to develop rapidly in the postoperative period. If metastases are not apparent after this period, presumably a biologically inactive neoplasm has been present and prognosis is thus favourable regardless of the hormonal changes that occur with the pregnancy.

It is in the treatment of metastatic disease that œstrogen deprivation does have a very real place; once again, certain concepts will be pre-

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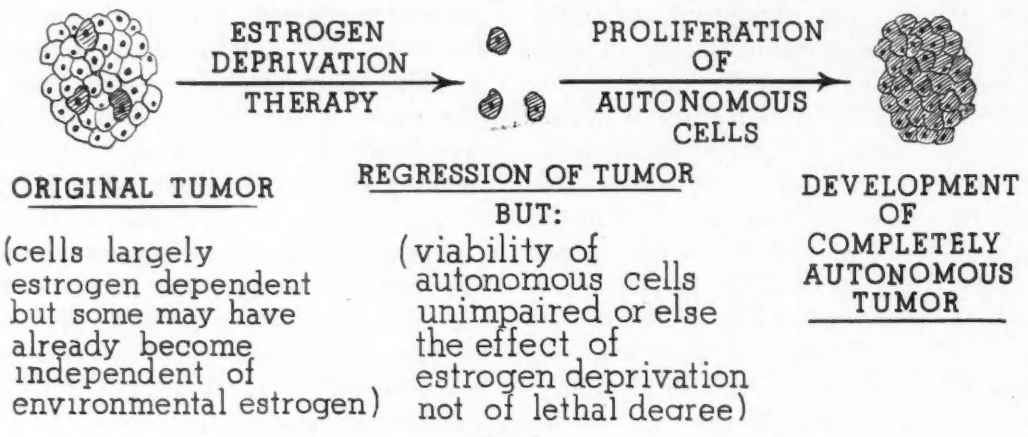

Fig. 5

sented in order to place this mode of attack on a rational basis. In the first place, if œstrogen is the main factor responsible for establishing a favourable situation for the proliferation of these neoplastic cells, one could reasonably expect its withdrawal to cause regression of the lesion. However, although many do respond, some fail to be affected, and even those that do show response have eventual recurrence of disease. To explain this paradox the concept of dependency and autonomy (Fig. 5) has been devised, expressing the theoretical possibility that all the malignant cells require œstrogen for their initial growth but as they gain in biological activity are able to compete for vital substances even without this favourable factor in their environment, thus being able to continue to proliferate freely when it is withdrawn. By the time the disease is recognized in metastatic sites at least some cells have already proven their invasive potentially and will likely be independent of œstrogen support, even though the major mass of the neoplasm may be comprised of cells still sensitive to œstrogen and dependent upon it for further growth. These cells will therefore, without effective support, succumb to the competitive activity of the host cells, quite possibly with disappearance of all clinical evidences of residual disease. Some autonomous cells, however, will remain which are capable, on continued growth, of producing once again the evidences of persistent disease resulting eventually in denial to the host of its metabolic requirements and a fatal termination.

Therefore, œstrogen deprivation can only be prescribed as palliative therapy and the palliation must be worthwhile in order to warrant its use. In the young patient the major source of œstrogenic material is, of course, gonadal and the effects of deprivation can be adequately assessed by simple castration. In the older patient the major source of œstrogen is probably the adrenals, although much evidence, both histological and pathological, exists to indicate that some ovarian function also persists in postmenopausal women. Castration in these instances must be accompanied by adrenalectomy in order to complete eradication of all sources of this hormonal stimulus to continued growth. Castration in both groups is preferably of surgical type, as the variation in response of ovarian tissue to radiotherapy makes the effectiveness of radiation castration difficult to assess.

As castration alone is a relatively innocuous surgical procedure, it can be advised with some conviction when other established methods have failed, particularly since it produces remissions, in slightly less than one-half the patients treated, for a period varying between six and nine months. This would appear definitely worthwhile, but when one contemplates the addition of adrenalectomy, the decision becomes much more difficult. Of premenopausal patients re-

sponding to preliminary castration, better than one-half are reported to have an additional remission after adrenalectomy, of approximately the same length, so that about one-quarter of the original group may show a favourable response for a period averaging between 12 to 18 months. According to the Memorial Hospital group,[21, 22] none who fail to respond to castration have a favourable result from adrenalectomy, and one would doubt that any indication exists for its use in these patients. Despite the necessity for continuous cortisone therapy postoperatively, the fact that information of a prognostic value can be obtained by such a simple means as oophorectomy does, we think, allow one to consider the procedure in favourable candidates; particularly when the patient, fully cognizant of the nature of her disease and of the operative possibilities, is willing and indeed anxious to take the estimated gamble of prolonging her useful existence in order to attend further to family responsibilities or personal needs. Certainly one cannot urge such a procedure. The decision must largely be one made by the patient and her family, varying as it will with the individual's reaction to the approach of a fatal termination.

In the older age group, in whom adrenalectomy must be performed without any preliminary information concerning the possible value of œstrogen deprivation, the decision becomes still more difficult as the operation is of greater magnitude and undertaken usually in a patient with less tolerance to surgical insult. The patient too more frequently feels that the normal span of her life has been almost spent in any case, and she is therefore not favourably disposed to the gamble inherent in this form of treatment. Nonetheless, in those psychologically suitable, objective improvement is noted in better than two-thirds of the patients, and of a duration in those responding favourably probably exceeding nine months on the average. Such results cannot in this type of patient be completely ignored.[26]

When one attempts to predict the value of adrenalectomy, the only factors affecting the prognosis favourably appear to be the clinical duration of the patient's disease since its original clinical recognition—a lengthy history suggesting biological inactivity and the possibility of response to any inimical factor; and the location of the metastatic disease—objective change being most frequent in osseous metastases and local soft tissue recurrences. When vital organs such as the lungs, liver, or central nervous system are involved, regression is less frequent and the remission often of such short duration that one would hesitate to consider even the initial favourable response to be worthwhile. One might therefore consider advising œstrogen deprivation in a young woman further assessed by surgical castration, who has been found to show a favourable response of adequate duration, and in patients of all ages who, acknowledging the gamble inherent in adrenalectomy, wish to do everything in their power to prolong their useful existence. The fact that in approximately one of every three patients subjected to total œstrogen deprivation there is a dramatic response characterized by prompt relief of distressing or disabling symptoms, objective regression often amounting to clinical healing of metastatic areas and, therefore, restoration of the patient's ability to live her daily life in a relatively normal fashion, makes this a form of treatment that cannot be completely abandoned at the present time in these suitable candidates.[26]

Actually the final word has not been written even at this point in the possibilities for therapeutic attack upon the disease. The ovaries and the adrenal glands have already been implicated, and it seems reasonable therefore to complete our consideration of the pituitary-gonad-adrenal axis, long appreciated as of fundamental importance in hormonal balances. Cramer and Horning[27] demonstrated 20 years ago that hypopituitarism could be produced experimentally by prolonged œstrinization. The concept of reciprocal endocrine relationships presented in Fig. 6 is again a practical means of clinical assessment of further alternation of this axis, depression of pituitary function being obtained either by hypophysectomy or by the administration of large doses of cortisone or œstrogen (and quite possibly testosterone as mentioned above), which lower the physiological demands for continued production of the adrenocorticotrophic (ACTH) or gonadotrophic hormones. The possibilities of œstrogenic therapy have already been considered. Cortisone therapy in large doses (200 to 400 mg. per day), having the same theoretical basis, might be expected to have very similar results. This is in fact apparently true, with objective remissions reported in nearly one-third of patients so treated, although tending to be of very temporary duration.[22] The

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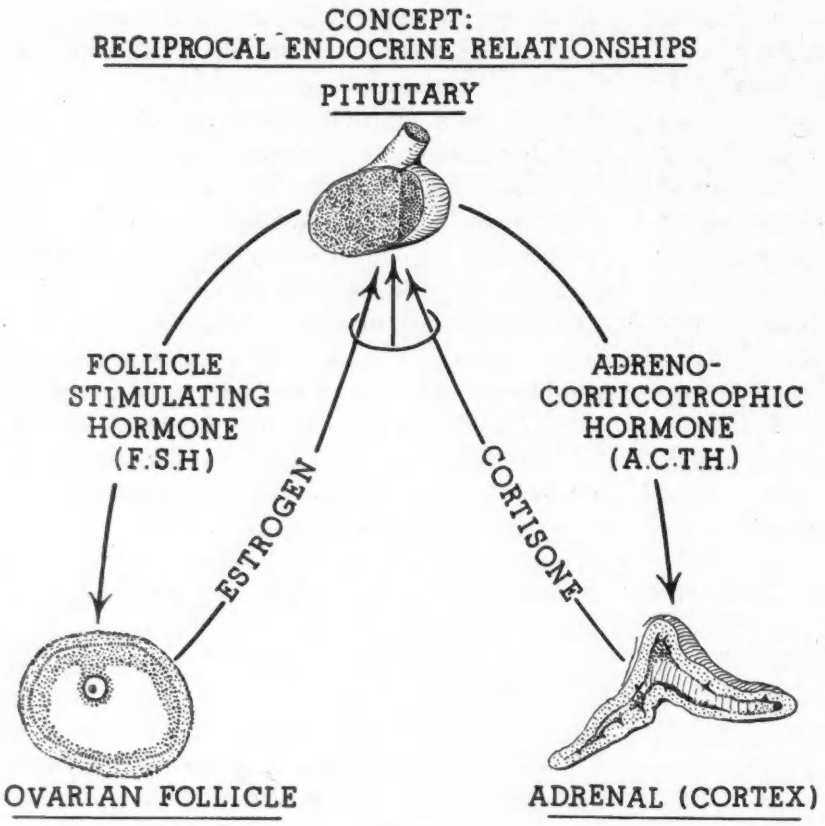

Fig. 6

effectiveness of this form of "medical adrenalectomy" has led some to discontinue further evaluation of the surgical method, although the occasional dramatic and prolonged responses obtained in the latter procedure have not been reported following cortisone therapy, and indeed a sufficient number of cases have not yet been assessed to allow firm conclusions to be drawn. Therefore, we prefer to use cortisone when adrenalectomy is not indicated or has been refused by the patient, and when adrenalectomy has failed to influence the course of the disease or when reactivation has occurred after a post-operative remission.

Whether or not actual hypophysectomy should be considered is even a more difficult problem in surgical judgment than the decision regarding adrenalectomy. If radiotherapy, androgens, œstrogen deprivation and pituitary depression have been attempted beforehand, the patient's emotional responses as well as her physical reserve will surely have approached the limit of endurance. Few will be still receptive psychologically to the thoughts of further serious surgical treatment when all previous attempts at control have been in vain, despite the fact that effective palliation may have occurred for an appreciable length of time from one or other of these previously applied techniques. Wearying of the almost unbearable emotional stress of alternate hope and disappointment, most will be resistant to any suggested plan of this kind, and further attempts to give the patient security and confidence that she might yet lead a useful life will be of no avail. The important consideration, then, at the moment lies in the attempt to determine whether hypophysectomy alone might produce results identical with the total result achieved in the combination of methods of hormonal alteration previously listed. If so, one would have to expect successful palliation in favourable cases amounting to about two years or longer in order to encompass the period of relief achieved by œstrogen deprivation, androgenic therapy and pituitary depression by medical means. Although Treves[28] is now able to report on 34 cases of which eight had a favourable response (with five additional cases yet too early to evaluate) and in which the operation seems to carry little risk, with a reasonable expectation of total functional ablation of the pituitary gland, one cannot yet be certain that this period of relief will be obtained. It would, therefore, appear to be therapy likely to add to the physical burden of the patient, necessitating as it does the operative insult to the psyche, the operative risk, the possible danger of sacrificing one optic nerve, and the necessity for postoperative replacement therapy without reasonable assurance of commensurate benefit. In those patients who cling to a slender life-line with indomitable will and who desperately desire that all possible methods be taken to prolong their life, the procedure warrants trial and it may yet prove of greater value than we think at present.

The exact mode of action of hypophysectomy is not at all clear, as it affects a great variety of functions by its hormonal implications. The fact that Graham[29] has found accessory adrenal cortical tissue in 33 of 100 consecutive autopsies, and that Treves reports two of 12 patients to be

capable of surviving without replacement therapy after adrenalectomy, certainly suggests that pituitary resection may be effective through its suppression of all remaining adrenal cortical function. Then, too, the Memorial Hospital group have reported[22] a case in which a remission was obtained after hypophysectomy and in which growth hormone produced reactivation of the osseous metastases with remission again after withdrawal of the growth hormone, suggesting another possible mode of action. Whether other factors act in this complicated readjustment will need further appraisal.

Finally, the experimental field of investigation in cancer research cannot be excluded from this discussion, for it surely affords the brightest prospects of eventual control of malignant disease. Many fundamental factors have been elucidated, and although some are undoubtedly difficult for a clinician to appreciate, the possibility of their clinical application is always a beacon lighting the way to further investigation of both clinical and experimental types. Cancer research actually has been concentrated for the past few decades on the problems of carcinogenesis by chemical or physical agents; the metabolism of malignant tissue and the possibility of affecting it by chemotherapeutic agents; the infective or virus hypothesis; and the antagonistic factors of biological activity in the tumour cell and resistance or immunity in the host. There has been much clinical interest in the possible importance of eliminating carcinogenic agents from our environment, but too little emphasis has been placed on some of these other factors. For instance, definite differences in carbohydrate, fat, and protein metabolism are apparent in animals bearing malignant tumours, the low concentration of various B vitamins possibly affecting the efficiency of the release of energy in carbohydrate metabolism and the normal processes of protein metabolism. Then, too, as McHenry[7] points out, glutamic acid levels in plasma are more than twice normal, this amino acid being one of the most important bases of protein anabolism. In addition, lipæmia is common in tumour-bearing experimental animals who are fed large amounts of fat, possibly due to uncontrolled catabolic activity which makes it impossible to store the fat ingested as a normal animal will.

Actually much interest is again centred upon the infective hypothesis as the pendulum swings back to the virus theory of tumour development. As is natural, there have always been some who believed that cancer, a progressive condition inimical to the body as a whole, is due to some external agent capable of sustained action; and to assume that this agent lives and multiplies in the growth appeared the best means of explaining its persistent effect. Rous[30] in 1911 discovered for the first time that a sarcoma from a Plymouth Rock hen could be transmitted by a cell-free Berkefeld filtrate, and other similar lesions have since been discovered. Andrewes[31] in 1931 confirmed the existence of an antibody in Rous filtrable tumours, by mixing the serum of tumour-bearing birds with active filtrates, with the result that injection commonly failed to produce a tumour. Subsequently, antibodies comparable to those operative in microbial infection have been demonstrated in several transplantable tumours which immunize the host. By 1931, Lumsden[32] found that serum of rats given repeated intraperitoneal injections of a suspension of the Jensen rat sarcoma destroyed tumour cells but was innocuous to normal rat cells in tissue culture. Finally, in 1937 Lumsden and Phelps[33] showed that the concentration of this cytotoxin in the serum of tumour-bearing rats in which regression subsequently occurs was greater than in other animals with the tumour. This suggests that the production of a cytotoxin is the mechanism whereby spontaneous remission is brought about, and also the possibility that the antigenic differences between the host and the malignant tissues might be sufficiently great to stimulate antibodies adequate to ensure such disappearance even in the instances of spontaneous cancers. Clinical observation of spontaneous regressions of frankly malignant lesions has long puzzled clinicians, being attributed recently, in mammary carcinoma at any rate, to the possibility of autoadrenalectomy in view of the frequency with which extensive adrenal metastases are discovered at time of adrenalectomy (58% in our series);[26] but similar changes have been observed in other tumours and the immunity factor may well be the deciding one in such instances.

The possibility of applying these observations clinically has recently been explored by Murray[34] but, as yet, no opinion is available as to the value of such immune sera. Rous and Kidd[35] in 1936 showed that carcinogenic agents might affect cells in a preparatory manner, rendering

them more susceptible to the subsequent action of a virus, and offered the hypothesis that when a tumour is induced by applying carcinogenic agents the vital change from hyperplasia to malignancy is probably associated with the entry of a virus, presupposing the widespread existence within the animal body of such viruses of low infectivity but capable of this synergistic activity. Clinically, precancerous lesions might have some such life history. Pentimalli[36] has demonstrated that immune bodies which neutralize the viruses of avian neoplasms appear in the blood of a high percentage of apparently normal fowls more than 18 months old, and are presumably formed in response to the presence of a virus related to, or identical with, the virus found in actual neoplasms. These reports are all of long standing, and the fact that little is still known of their significance indicates the difficulty encountered in the clinical application of such results, which are almost invariably specific for the animal species studied. It is only recently that infective agents have been demonstrated in human neoplasms by the use of special cultural media, and great hopes are held that this field may yet open up into one of clinical importance. Certainly, in spite of all assertions by sceptics that animal tumours are not comparable with neoplastic disease in man, experimental cancer research has built up a system of knowledge that could not have been procured by other means.

A REGIMEN OF THERAPY IN METASTATIC MAMMARY CARCINOMA

As in the case of the primary lesion, these numerous possibilities for therapy in patients with metastatic mammary carcinoma make it necessary for one to have a plan of treatment from which to draw the proper advice depending upon the extent of the dissemination and the organs involved. One such plan is summarized as follows:

1. Established methods of irradiation are still by all odds the most effective when the commonest types of metastases involving the skin of the chest wall, the osseous system, and the accessible lymph nodes are present. They may be advised with firm confidence in their ability to afford palliation in its truest sense.

2. In large pleural effusions and ascitic collections requiring frequent aspirations for comfort, the instillation of effective amounts of radioactive colloidal gold similarly affords palliation of real value.

3. In lesions not suitable for a radiotherapeutic attack one must resort to agents affecting the disseminated lesions via the blood stream.

Because of the importance of hormonal factors, and particularly œstrogens, in favouring the continued growth of the neoplasm, one can practise œstrogen deprivation or androgen addition. Because œstrogen deprivation is more effective, surgical castration should be the first step in premenopausal patients, and if a satisfactory remission is obtained adrenalectomy considered when reactivation of the metastases appears. In the older women, because œstrogen deprivation implies simultaneous oophorectomy and adrenalectomy, without any information regarding the likelihood of its success, we favour androgenic therapy although its effectiveness in no way reflects the potentiality of œstrogen deprivation. If testosterone is ineffective, or when it proves no longer of value, œstrogenic therapy may be attempted with cautious attention to its complications. Subsequently, adrenalectomy may be advised in suitable patients with long clinical histories, metastases involving bone and superficial soft tissues, and preferably a previous favourable response to irradiation. Only in psychologically ideal candidates anxious to accept a gamble the implications of which they are fully aware of, is this procedure otherwise considered.

4. Following œstrogen deprivation, androgenic therapy may still be advised in those in whom it has not been previously assessed.

5. When other methods fail, large doses of cortisone or pharmacological dosage with œstrogens (preferably in postmenopausal women only) may be attempted, presumably with a view to effecting pituitary depression.

6. Hypophysectomy at the moment is restricted to those who retain a favourable outlook to further major surgical attack after all previous therapy has eventually failed. However, the important feature of this procedure, not yet assessed, is the determination of its potentiality to equal the combined results of œstrogen deprivation, androgenic therapy, and attempts at pituitary depression by cortisone and œstrogenic substances.

7. Immunological control and use of metabolic antagonists are as yet purely experimental but offer great unexplored fields for further investiga-

tion and provide hope for the eventual discovery of effective therapy of still more fundamental nature.

SUMMARY

1. Modern concepts underlying the treatment of mammary carcinoma are reviewed, with an attempt to place present methods of therapy in their proper relationships.

2. Treatment programmes are outlined for the management of the primary lesion and of metastatic disease. One must realize that cure can only be obtained in those with "curable" disease of biologically inactive type. Nonetheless, excisional therapy is still indicated in primary mammary carcinoma in order to effect cures in these fortunate patients, accepting the fact that metastases will subsequently become apparent in those unfortunate enough to harbour an invasive neoplasm.

3. Emphasis is laid upon the necessity for tempering surgical daring with mature philosophical judgment in the decision regarding the therapeutic regimen advised. This is particularly true when one is faced with a patient with signs of metastatic disease. In these patients any treatment must attend the precepts of Hippocrates, avoiding at all costs the danger of adding further to the burden for the patient by the procedure advised. Palliation must be effective in relieving the patient's suffering and restoring function with a reasonable expectation of an adequate increase in the survival period.

4. Nonetheless, one must not resort only to symptomatic treatment in this disease, for many different agents are now available which may be effective in temporary control of the neoplastic growth. Each reprieve is accepted with grateful appreciation by the patient whose tenacious grasp on a fragile life-line can only be expressed by those who have actually felt the spectre of death hovering overhead. The simple gratitude of those having worthwhile remissions after such major procedures as adrenalectomy demands further attempts to enlarge upon the possibilities of similar therapy while awaiting discovery of more effective means of control.

5. The time has come when unreasoning emphasis upon cure in cancer treatment generally should be replaced by intelligent attempts to provide the patient with relief from her subjective complaints, utilizing procedures fulfilling the requirements of satisfactory palliation. The practice of surgery should imply the treatment of persons and not merely disease processes, reemphasizing the fundamental importance that the doctor-patient relationship plays in this practice.

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RÉSUMÉ

L'excision radicale pratiquée depuis le début du XXe siècle constitue le traitement classique des lésions néoplasiques primaires. Bien que le cancer du sein soit dans un site idéal pour une intervention chirurgicale, la survie de 5 ans des malades opérées dépasse à peine celle des malades laissées à elles-mêmes. Le professeur McKinnon a depuis longtemps attiré l'attention sur cet état de choses, qui sert à illustrer l'énigme chirurgicale qu'une lésion étendue et négligée pendant longtemps peut quelquefois offrir un meilleur pronostic qu'une petite lésion traitée dès le début. Le dénouement dépend beaucoup plus de la nature du néoplasme que du traitement recommandé. Dès le début, un combat s'engage

entre la malade et sa lésion. Celle-là cherche à ériger une barrière de tissu conjonctif pour isoler celle-ci, qui, en retour, cherche à s'échapper par envahissement direct ou par l'entremise des vaisseaux sanguins ou lymphatiques. Tout ce qui peut influencer favorablement l'issu de ce combat constitue l'un des champs d'action les plus logiques et féconds de la recherche sur le cancer.

Si l'on accepte la théorie des trois stages dans la progression d'un néoplasme, à savoir: extension locale dans les tissus adjacents, infiltration de ces tissus ainsi que des canaux lymphatiques, et enfin, pénétration des veines avec dissémination par le sang (ces trois stages s'accomplissant à l'échelle microscopique), il devient évident qu'une lésion clinique de 1 à 2 centimètres de diamètre a depuis longtemps selon toute probabilité dépassé la troisième étape. Cependant, les survies de 10 ans ou plus que l'on voit malgré l'envahissement des ganglions lymphatiques, laissent supposer que le troisième stage peut tarder pendant longtemps. L'excision d'une masse de son sein, en plus d'assurer à la malade une certaine survie probablement accrue, lui confère un avantage psychologique important en la débarrassant de la cause évidente de sa maladie, même si les effets occultes demeurent. Certains auteurs dénoncent la mastectomie radicale comme inutile sous prétexte que, si les ganglions sont intacts, mieux vaut les laisser et que, s'ils sont envahis, leur dissection peut stimuler la diffusion des cellules cancéreuses et accélérer le développement des métastases. Les résultats obtenus, particulièrement dans les lésions du stage II, ne semblent pas justifier ces craintes. La mastectomie simple pourrait se prêter à ces critiques; cependant, si elle est suivie de radiothérapie en doses suffisantes, ses résultats se rapprochent de ceux de la mastectomie radicale sans toutefois en avoir les inconvénients. L'emploi de radiation préopératoire offre aussi l'avantage de diminuer l'activité néoplasique, de créer une obstruction à la circulation lymphatique par l'entremise de la fibrose et de retarder ainsi la dissémination des cellules cancéreuses.

Quelle que soit la technique opératoire employée, si les ganglions lymphatiques axillaires sont positifs, la radiothérapie doit inclure les trois réseaux (aisselle, médiastin, mammaire interne) à cause des communications qui existent entre eux. La dissection de la région axillaire peut être complétée sans enlever les muscles pectoraux; les récidives locales n'en semblent pas plus fréquentes, dans les cas précoces.

Les sites habituels de métastases du cancer du sein sont: la peau de la poitrine, les os, surtout de la colonne vertébrale, et les poumons. Plus les métastases tardent à paraître, moins le pronostic est sombre. La radiothérapie, aux endroits qui lui sont accessibles, offre un apport précieux. L'instillation d'or radioactif dans l'espace pleural ou la cavité péritonéale peut juguler les métastases qui s'y trouvent. La testostérone à raison de 300 mg. par semaine donne lieu à un soulagement symptomatique dans la moitié des cas et, dans 20%, cette amélioration peut s'observer objectivement. Dans certains cas, au contraire, l'état général se détériore et l'amélioration est apportée par les estrogènes, chez les femmes ayant dépassé la ménopause. Dans les cas où l'on doit tarir la source d'estrogène, une castration radiologique ou chirurgicale peut être effectuée, combinée ou non avec une surrénalectomie. Ces interventions ne doivent pas faire partie d'un programme de routine comme certains auteurs l'ont déjà suggéré, car il est certainement des cas où elles ne sont pas nécessaires, comme le prouvent ces femmes devenues enceintes après mastectomie et chez qui la survie n'a pas été écourtée. La surrénalectomie s'avère utile dans plus de deux tiers des malades passées la ménopause. Chez les femmes moins âgées, il est plus sage d'évaluer d'abord les résultats apportées par la castration avant de soumettre la malade aux risques que comporte la surrénalectomie. Il y a déjà plusiers années que l'on cherche à obtenir une hypophysectomie médicale en déprimant la fonction de la pituitaire au moyen de fortes doses, maintenues pendant longtemps, d'estrogènes, de cortisone, voire même de testostérone. L'intervention chirurgicale donne tout de même des résultats plus catégoriques; cependant la malade arrivée au stage où cette opération est envisagée l'accepte difficilement. L'importance du procédé tient au fait que dans 33% des cas, il existe du tissu surrénal aberrant. La suppression de l'hormone de croissance n'est pas à négliger. L'auteur mentionne aussi le facteur immunologique dont le problème est encore à l'étude.

M.R.D.

LIMITATIONS IN DIAGNOSIS AND TREATMENT OF BREAST AND OTHER CANCERS*

A REVIEW

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RECENT ANALYSES[1-3] purporting to show that treatment of breast cancer prevents death in a very considerable proportion of cases or that early treatment is greatly superior to later treatment in this regard point the need for further consideration of some of the fundamental limitations in both the diagnosis and treatment of cancer.

The basis for treatment of breast cancer is, as everyone knows, the premise that, in the great majority of cases, spread is at first to regional lymphatics and then to remote sites, with sufficient time elapsing between the first manifestations and the spread to permit eradication of the lesion in many cases before the axillary lymph nodes become invaded and well before remote spread occurs. Although it is often assumed that this premise is factually established, that is not so. Harrington himself has been at pains to point out[4] and reiterate[5] that it is *hypothetical* in nature. "If this conception of the disease is correct," he says, then early and complete treatment is of paramount importance, but in an analysis of over 8,000 cases[5] he fails, as shown later, to provide unequivocal evidence of its validity. On the other hand,

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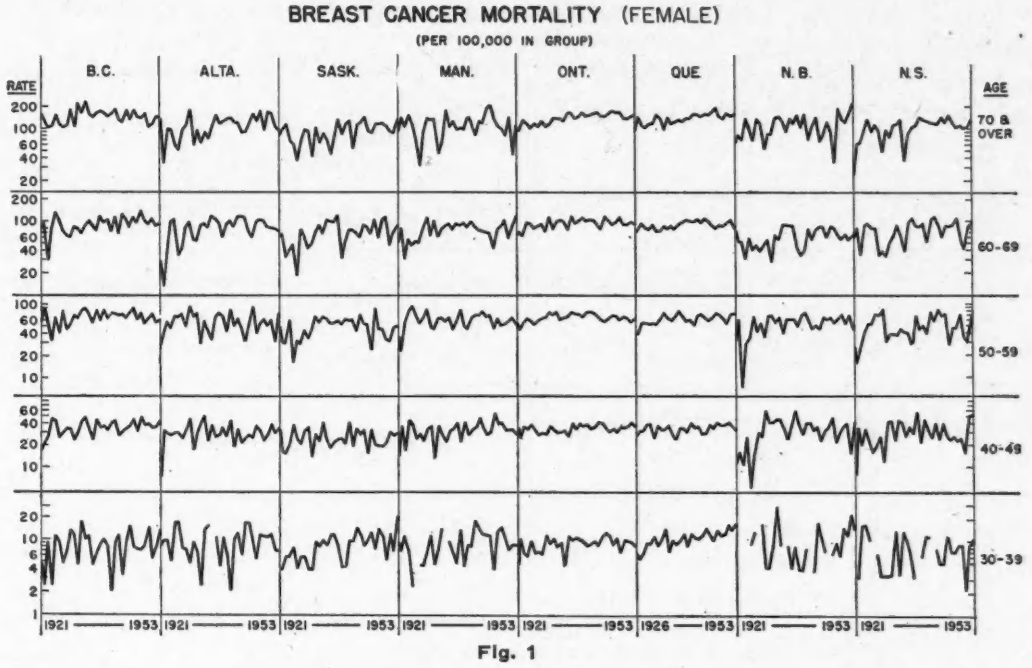

Fig. 1

examination of pertinent evidence from all fields—statistical, anatomical, pathological and clinical—has shown that the premise is not merely hypothetical but fallacious. That evidence is reviewed here.

VITAL STATISTICS†

Breast cancer is, of all major cancers, the most accessible for early diagnosis and extensive treatment and the one therefore held to be most susceptible to control. Furthermore, with its local manifestations inescapable in practically all the cases and the manifestations of its remote lethal metastases well recognized for the past 30-35 years at least, the error in the diagnosis of breast cancer in death certification over those years should be less than in any other major cancer. In the accompanying graphs there are the recorded age-specific mortality rates for breast cancer for eight of the Canadian provinces (Fig. 1), and for Massachusetts, New York State, Connecticut, Minnesota, Missouri, England and Wales (Fig. 2), and New York and Denmark (Fig. 3). Here it is seen that, with the exception of those for the older age groups, the rates maintain fairly level trends as their most constant and conspicuous feature. Although an occasional rate has fallen or otherwise diverged from the general pattern, the fall or other divergence is not consistent with the trends in other age groups in the same place, or is not maintained, or is not correlated in time and place with control efforts and earlier treatment, or is demonstrably attributable to a change in bookkeeping. But it has been contended that the primary data, death certificates, are too lacking in accuracy[2] and the bookkeeping is too unrealistic for the trends derived therefrom to be given any credence. In an investigation of the accuracy of recorded cancer mortality, Dr. Herbert L. Lombard, Director, Division of Cancer and Other Chronic Diseases, Department of Public Health, Massachusetts, examined hospital records and questioned the physicians supplying the death certificates in that State in 1932. By that means he found the recorded breast cancer mortality deficient by 10% through deaths actually due to breast cancer being classified in other categories. In 1939, the deficiency was 5% and at the time of the report, 1952, it was less. Dr. Lombard attributed the decrease in the deficiency, from 10% in 1932 to 5% in 1939 and to less later, to improvement in classification.[6] Such improvement in diagnosis, certification or bookkeeping is plainly reflected, as has been pointed out previously[7, 8] in the increase in the rates *for older age groups* in Massachusetts and in other places. But, as

†The data have been drawn for the most part from official Reports of Vital Statistics but for some I am greatly indebted to Dr. Herbert L. Lombard, Boston, Massachusetts; Dr. Paul R. Gerhardt, Albany, New York; Dr. J. V. DePorte, Albany, New York; Mr. Clyde A. Bridger, Jefferson City, Missouri; Mr. J. W. Brower, St. Paul, Minnesota; Dr. Henry Hamtoft, Copenhagen, Denmark; and Mr. H. G. Page, Ottawa, Canada. My thanks are due, too, to Dr. Selwyn Collins, Washington, D.C., for kindly providing post-censal, colour, sex and age estimates of State populations, not otherwise available.

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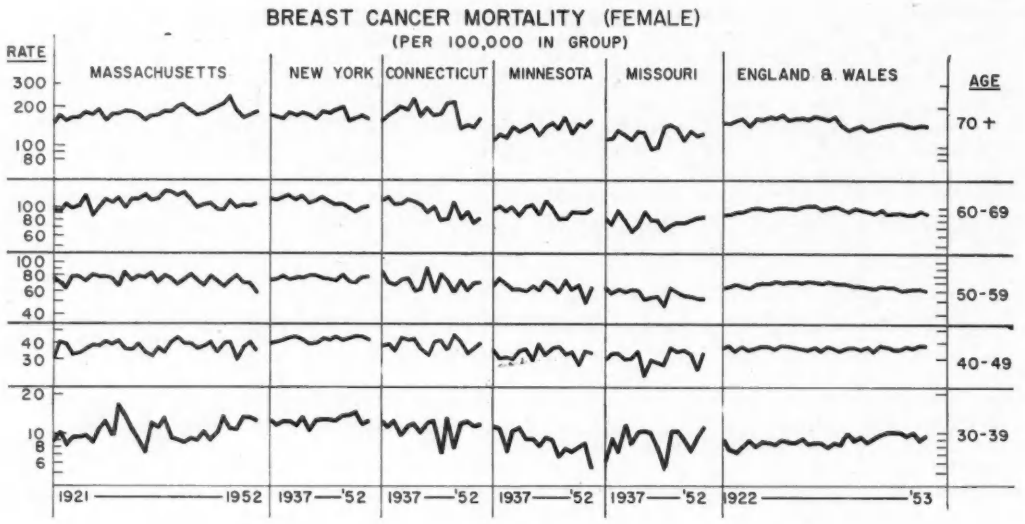

Fig. 2

far as the rates show, this change is practically confined to older age, the rates for those who had not reached that period of life and who supply the larger part of breast cancer deaths being little, if any, affected. Confinement of improvement almost entirely to the older age groups is not at variance with what might be expected from clinical and pathological considerations. Certainly with the deficiency in the total rate of the limited extent noted, the deficiency in the rates for those below old age would be very much less and thus not sufficient to influence the general lie of the lines to any appreciable extent. If, on the other hand, the mortality charged to breast cancer in the age groups below old age included, through vagaries in diagnosis, certification or bookkeeping, any material proportion of deaths due in reality to other causes, those rates would show: (a) a slight decline due to the real and marked decline in mortality from causes other than cancer in those age groups; (b) a change coincident with a change in selection of cause of death.* The fact that the rates (under old age) do not, in general, exhibit either of these features is substantial evidence, challenging contradiction, that they have not included any material proportion wrongly charged to breast cancer. However, the precise degree of accuracy is bound to vary somewhat not only with age but also with time and place, and absolute accuracy for any age group for any place for any time should not be expected.

But breast cancer mortality under old age has remained practically steady, as noted, in each of the Canadian provinces despite vast differences between the control programmes and changes in some of them, and with the bookkeeping of all the provinces done by the Dominion Bureau of Statistics, and a similar tendency is noted in that mortality in other places despite vast differences between control programmes and changes in some of them, but with the bookkeeping under different auspices, and in some, a change in selection of cause of death.* This steady state of recorded mortality is not what would be expected from rates influenced to any considerable extent by extraneous factors. It cannot be the result of chance, or of an increase in the incidence of breast cancer equalling and offsetting mortality reductions of different magnitude, or of artificial increases (through changes in diagnosis, certification or bookkeeping) varying so as to offset such reductions. These levels, in themselves, refute the criticism[2] of the rates that has been made in excuse of the lack of declines in the recorded mortality. They fairly establish, in themselves, that the rates *for those below old age* have been relatively uninfluenced by extraneous factors and closely approach reality. This persistence of uniform level trends in rates derived from such diverse and changing circumstances thus leaves no doubt that control programmes providing earlier and more treatment have not achieved any decisive reduction in that mortality. On critical consideration,

The selection of the single cause of death from multiple causes was changed from the bookkeepers' responsibility, based on specified priorities, to the responsibility of the certifying physicians on the basis of their own opinion in England and Wales in 1940, in the U.S.A. in 1948 and in Canada in 1950.

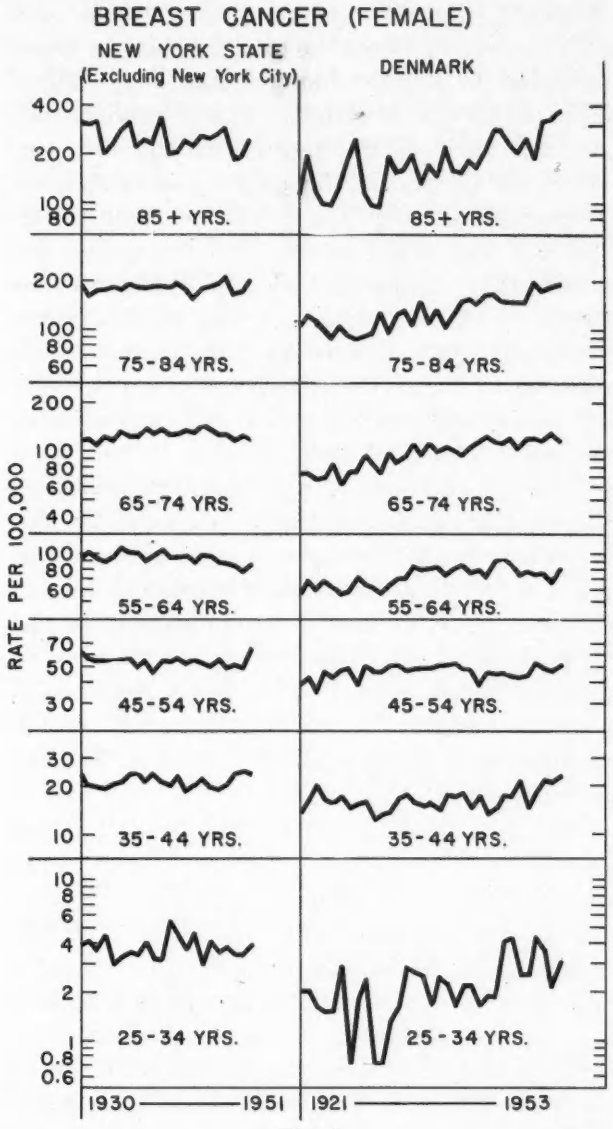

Fig. 3

then, of all pertinent factors — the rates from different and changing sources, the varying provision of diagnostic and therapeutic services, the different degrees of increase and speeding up in treatment, the inconsistencies and contradictions in reported results and in rival claims for different techniques, the indubitable failures in indubitably early cases, the nature of the disease and the anatomical relationships (vertebral venous system[9]), the recognized diagnostic difficulties in borderline cases,[10] etc. — it must be postulated that in most, if not all, lethal breast cancer the remote metastases that are the eventual cause of death are spread *from the primary lesion via the blood stream* before the lesion can be detected and treated. This deduction obviously clashes with the premise on which treatment and control programmes were based and it implies that neither early nor extensive treatment of the primary lesion with its lymphatic drainage areas can materially reduce the mortality. And the lack, as far as is known, of any specific influence of the primary lesion on the development of metastases after their implantation excludes, albeit tentatively, the possibility of specifically *postponing* death by locally successful treatment of the primary lesion and its regional foci.

Some emphasis has been laid on the development of cancer from "precancerous" states.[11, 12] It might be contended from this that the attack on cancer in the hope of reducing mortality should be carried further back to such conditions. However, as many of the programmes that have failed in the control of cancer mortality have included vigorous attack on all lumps and conditions considered possibly "precancerous", any such contention would appear to be advocacy of what has already failed and of what would lead to ever-increasing treatment with further loss of breast tissue but without any commensurate or even material reduction in mortality.

In view of the near universality of the belief in early treatment and the data supporting it, re-examination of these data becomes obligatory.

Fallibility of Data Purporting to Show That Early or Extensive Treatment Prevents Death

Higher survival rates for shorter than for longer pre-treatment duration in cases diagnosed and treated under the same auspices at the same time have been advanced as evidence of the superiority of early treatment.[3, 13] Such higher survival rates for cancers of shorter duration are not found consistently, however, even in single series over all durations or in successive series from the same clinic. For instance, Haagensen and Stout found a decrease in survival rates with increasing durations, *for a period*, in their 1915-34 cases,[13] but no such decrease in their 1935-42 cases.[14] Their failure to find a decrease in the later series is not by any means unique; others record similar observations.[15-17] However, even if a decrease in survival rates with increasing duration were found consistently, it would not be conclusive evidence of the superiority of earlier treatment, because patients with untreated lethal cancers of successive durations (*for a period*) have shown decreasing sub-

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sequent five-year survival rates. (As will be shown later, the pattern of mortality and survival of any series is dependent on the distribution of different types of cases in that series.) Thus, a decrease in survival rates with increase in pre-treatment duration cannot be attributed confidently to delay in treatment.[18]

But the more common data supporting belief in early or otherwise different treatment are the higher five-year survival rates obtained in some series than in others and attributed to differences in time or type of treatment, and the *most* common supporting data are the high five-year survival rates obtained regularly in stage I (confined to breast) cancer. In regard to the latter it cannot be too strongly emphasized or, apparently, too often repeated that stage I cancer is *not* cancer of short duration and should not be so misconstrued.[7] It was recognized years ago[19, 20] that developmental state and duration have no constant relationship but that stage I cancers include all durations, some very long, and cancers of allegedly short duration include all stages, some far advanced. As well as showing conclusively that stage I cancer is *not* cancer of short duration, the data of stage and duration regularly suggest, as will be noted later, that the difference between stage I cancer and cancer of other stages is largely one of type of lesion rather than of time; they suggest that many stage I cancers have little if any tendency to give rise to metastases and, if untreated, would not progress in weeks, months, or years, if at all, to other stages.

In further examination of the situation, consideration of two series of cases is instructive. In both series practically all the diagnoses were "proven" by microscopy. In one series, the five-year survival rate was 62.4%,[5] in the other it was 43%.[21] If the difference between 62.4% and 43% were due to difference in treatment, then, in fairness to the patients presenting at the clinic achieving only a 43% five-year survival rate, they should have been sent immediately and without interference to the clinic achieving the 62.4% five-year survival rate* or to the other clinics achieving similar or higher rates.† However, the difference between 62.4% and 43% is not attributable to difference in treatment but to another factor. Stage I constituted 50% of the series with the 62.4% survival rate and only 16% of the series with the 43% survival rate. Obviously, this difference between the proportions of stage I with its consistently high survival rates could readily account, though not necessarily exclusively, for the difference between 62.4% and 43% five-year survival rates. Obviously, too, comparison of these survival rates, or of others from different sources, without allowance for difference in distribution of the cases, could not yield and should not be expected to yield reliable information regarding the relative efficacy of treatment. Thus, the difference between the survival rates of these two series serves to demonstrate the spurious quality of the support derived from comparison of survival rates of two or more series differing in time or place, especially of series selected on different bases,[1, 3, 21] even though either or both of the series compared be "proven" through microscopy.[23]

But these two series of cases pose another problem that is, perhaps, not so obvious: How can the difference between 50% and 16% in the stage I proportions be accounted for? The only reasonable explanation, free from fantastic and therefore invalidating assumptions, is that it is due to difference in diagnosis, the former series including, as cancer, lesions which were excluded from the latter series as not cancer. And the fact that very few if any of the patients who were excluded, at first presenting, from the latter series, and were not treated as if they had cancer, returned later with obvious cancer shows that *progressive* cancer was not missed in the diagnosis of this series; on the other hand, there appears to be no reasonable alternative to the conclusion that the series with 50% in stage I must have included *non-progressive* cancers as the larger part of its stage I cases. Hence the

*The funds so freely contributed by the public and its agencies for the control of cancer mortality would surely have been available for this purpose.

†Delarue,(2) in supporting early treatment, noted that Eggers obtains a 76% five-year survival rate in patients treated with a delay of less than one month. However, the number of patients on which this figure was based was only 21. He quotes, too, Haagensen and Stout's survival rate of 54% in patients treated within two weeks of alleged appearance of the lesion. But this figure was based on only 50 patients so treated, and 50 patients with durations of two to four weeks showed a survival rate of only 34%, the 100 patients treated within one month having a survival of only 44% (quite a contrast to 76%) and patients treated in from one to six months a survival rate of 40%.(13) He could have quoted from a later study of Haagensen and Stout, as noted, to which he does refer to other purpose, wherein they did not find any difference between survival rates of those treated early and those treated later.(14) He could have noted, too, that Haagensen reports a 90% five-year survival rate for stage I cancers(22) while the Toronto clinic achieved only 81%.(21) And he could readily have quoted many other figures revealing similar inconsistencies and contradictions in breast cancer literature through, or in spite of, which belief is maintained.

microscope failed in a very considerable proportion of cases to differentiate between non-progressive and progressive "cancers." And the inclusion of the non-progressive lesions to this large extent obviously accounts, though not necessarily exclusively, for the excessively high five-year survival rate of 62.4% for the whole series; obviously too, it largely accounts for the high five-year survival rate of 85.6% in the stage I cases of that series.[23]

Here it may be noted that if all the stage I cancers in both series were non-progressive lesions, there would be no death from cancer in either of the stage I groups and the survival rates in them would thus be high and equal. The five-year survival rate in the stage I cases forming only 16% of the one series[21] was actually 81%. The near equality of this with the 85.6% and the similarity of both to the high rates usually obtained in stage I cancers point to similarity in the material from which the rates are derived. In other words, as the high survival rate in the stage I cancers forming 50% of a series was, as shown, attributable largely to the majority of them being non-progressive lesions, the high survival rates in most stage I cancers suggest that the majority of them are also non-progressive lesions.[24] This suggested explanation of the high survival rate in stage I cancers must then be checked for compatability with other breast cancer data.

Data of stage and duration[13-15, 25-28] consistently show that 50-60% of breast cancers of very short duration when diagnosed (within 4-6 weeks of alleged appearance) have already extended beyond the breast. They show too that the decrease in stage I, or conversely the increase in frequency of extension beyond the breast, at longer durations, is variable but always limited and rarely if ever sufficient to eliminate all stage I even at the longest durations. (The stage I state persisted in five out of 19 cases of five years' duration or more in Park and Lees's series.[27]) Other data show, too, that increases in the proportion of stage I cases in treated cancers did not reduce age-specific mortality rates.[7, 8] With these actual observations, which, it will be noted, do not fit well with the concept that all or most of stage I cancers would progress to other stages if untreated, the suggestion that the majority of stage I cancers are non-progressive non-lethal lesions is entirely compatible. At the same time the suggestion is compatible with and allows the reasonable criticism[29] that neither the data on duration nor those on axillary involvement are fully accurate or fully comparable from series to series; it is compatible with and allows the contention[17] that the high frequency of axillary involvement observed in cancers of allegedly very short duration may be attributable in part to such patients having a disproportionate number of highly metastatic cancers inducing early presentation, and that therefore the frequency of axillary involvement in such cases may not be representative of all cancer. The seeming paradox that only 50% extended beyond the breast in one of the series cited covering all durations[5] whereas 50-60% extended beyond the breast at very short durations in other series is fully explained, and consistently, by the demonstrated very high proportion of non-progressive lesions (as stage I cancers) in the former series. Although the grading of cancers has serious limitations[15] and, unfortunately, does not distinguish between non-progressive and progressive lesions, the hypothesis that non-progressive lesions form a majority of most stage I cancers fits well with the findings that the majority of grade I cancers are stage I, that the grade I form a larger part of stage I than of other stages and in some series a larger part of the lesions of long duration than of shorter duration, and that very high survival rates are regularly obtained in grade I–stage I cases, the lesions in the many patients who survive being indistinguishable microscopically from those in the few who succumb. The hypothesis is also compatible with and can reasonably explain the progressive increase in five-year survival rates in the stage I cases of series over successive quinquennia with progressively increasing proportions in stage I, and it is compatible with and reasonably explains, too, though not necessarily exclusively, the progressive increase in the over-all five-year survival rates in those series, as reported by Harrington.[5] It is compatible with and reasonably explains, though not necessarily exclusively, higher *five-year* survival rates in treated "proven" cases[1, 3, 21] than in untreated *lethal* cases (proven by death from cancer), and higher survival rates in some "proven" cases than in others treated by the same or different methods. It is fully compatible, too, with observations from the clinical field, as will be noted later, that treatment may be[28] or appears to be[30] ineffectual in preventing

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death; and, as noted, it reconciles that finding with, on the one hand, progressively increasing survival rates in successive series over the years and, on the other, the persistence of level trends in recorded mortality. Curing non-lethal lesions does not reduce mortality.

Thus, the suggestion that the majority of stage I cancers are non-progressive non-lethal lesions explains many of the conflicts and incongruities in cancer data and appears to be at variance only with the concept that "proven" (microscopically) necessarily indicates a progressive lethal lesion. The validity of that concept must therefore be examined from other angles.

THE EVIDENCE FROM PATHOLOGY

Pathologists generally recognize some difficulty and allow for some leeway in differentiating microscopically between the benign and the malignant in borderline lesions.[10] But it has not been generally conceded that the limitations of microscopy are such as would account for the difference between 16% and 50% in stage I, as cited, or would so drastically vitiate comparisons of different series. The figures, however, speak for themselves and, in view of their source, leave little doubt that diagnostic differences of like or even greater magnitude are relatively common. In considering this large difference in diagnosis, it should not be forgotten that although Halsted himself was acutely conscious of common difficulties and artefacts encountered in examining microscopical sections, some of his "cancers," according to Geschickter,[31] were found later to be benign adenosis. And Bloodgood, at the Halsted Clinic, pointed out in 1923 that, under the pressure of propaganda, cases were then presenting at the clinic which were different from those seen previously. While there was complete agreement among pathologists examining sections from what Bloodgood believed to be typically benign and typically malignant lesions, sections from these atypical cases were diagnosed as benign by some pathologists and as malignant by others. Bloodgood warned that the inclusion of such cases was then giving fictitious survival rates in some series and warned, too, that as time passed the proportion of such cases would increase and would increase the fallacy in survival rates. And he also warned that neither the public nor the profession should be deceived by these high survival rates, the excess in which could be attributed largely if not entirely to the inclusion of lesions of questionable character.[32] In the same clinic, in 1932, Lewis and Rienhoff demonstrated clearly and incontestably the inability of microscopy to reveal the biological nature—the metastatic or lethal propensity—of tumours. In illustration of this they cited two cases: In one, a lesion which had existed for 40 years was removed and the patient lived for many years afterwards; in the other, a small lesion of less than three months' duration was treated but the patient died within six months. Both lesions were scirrhous cancer; they were indistinguishable microscopically.[16] In 1941, Grace, who had early realized the inadequacy of microscopy as a basis for prognosis, reported investigations which he had made in tissue culture with the objective of obtaining better prognostic criteria.[33] In 1949, Urban and Adair showed that sclerosing adenosis, in sections, was still diagnosed frequently as cancer.[34] In 1953, Lewison, in the Halsted Clinic, re-examined the sections from patients surviving 10 years or more but found nothing which would have warranted a prognosis of the long survival that ensued.[35] As noted, in the so-called grade I—stage I cancers, the lesions in the few who succumb are indistinguishable microscopically from those in the many who survive. The many efforts that are now being made through grouping, grading, staging, combinations of these, tissue culture, and animal and egg inoculations, to obtain a more reliable basis for prognosis than microscopy provides, reflect in themselves not only the limitations of microscopy but also the recognition of these limitations by leading pathologists and clinicians. And a more general though more belated recognition of the limitations is reflected in the change in the *J.A.M.A.* In 1949, after H. S. N. Greene, Professor of Pathology at Yale, had frankly stated the case for the limitations and pointed out that it is not morphologists but others who confer "divinity" on morphology and "place the microscope on a pedestal and accept without question the muttering opinion of dead-house pathology",[36] the *J.A.M.A.*, while admitting that microscopy was not entirely infallible, severely castigated him and challenged his strictures.[37] In 1953, the same journal warned its readers of the need for caution in offering a prognosis and in appraising the results of treatment,[38] and in 1955, as noted, it even accepted

and published an analysis showing that, despite the many cures reported from many sources, simple and radical mastectomy appear to be alike ineffectual in preventing death.[30] Thus, the concept that "proven" (microscopically) means a progressive, lethal cancer is not compatible with factual findings or critical analyses in pathology and the clinic. Thus its incompatibility with the deduction that the majority of most stage I cancers are non-progressive non-lethal lesions adds to, rather than detracts from, the validity of this deduction.

DIFFICULTIES OF DIFFERENTIATION IN OTHER STAGES

The exposure of such limitations in the diagnosis of stage I cancer does not imply that the difficulties of differentiation are confined entirely to that stage. Patients with cancer of other stages, both untreated[16, 39] and treated,[16, 35, 40] have lived for 10, 15, 25 or more years without, or before, the appearance of remote metastases. As already noted, Lewison, in re-examining sections from tumours of patients who had survived 10 years or more, could find nothing in them to indicate such long survival.[35] In 1954, Williams, Murley and Curwen reported the same survival rate in cases that were clinically stage I but pathologically stage II (axillary involvement) as in cases that were clinically stage II but, on pathological examination, failed to show any axillary invasion. The survival rate in both was between those in stages I and II (clinically and pathologically).[28] While the equality of survival rates in their two groups, one 47 and the other 42 in a series of about 1,000 cases, could be due to the play of chance in the small numbers, it may indicate a degree or distribution of malignancy somewhat representative of the groups so identified and suggest some special significance in the character of glandular involvement. In fact, many experienced clinicians and pathologists recognize variations in malignancy associated with variation in character and amount of axillary involvement and take cognizance of both in estimating a prognosis. However, a progressive improvement in detection of lymphatic involvement in such cases as Williams *et al.* describe or in other types not yet identified could readily explain a progressive increase in survival rates in cases with axillary involvement over successive quinquennial periods, as reported by Harrington.[5] While grading, as noted, may give some guidance for prognosis in cancers with infiltration and regional or other metastases, it does not tally exactly with all the variations in survival time and thus does not resolve all the difficulties. (As the progress of a cancer probably depends in part on host factors, it is not surprising that grading of the tumour cells fails to account for all the differences in survival.) Obviously, therefore, comparability of malignancy (or survival time) even of cancers with extensive infiltration and axillary or other involvement cannot be taken for granted or assured; deductions drawn from comparisons[1, 2] of survival rates of such cases may be misleading and should, therefore, be received with due reservations.*

CLINICAL DATA

In the clinical field itself there are critical analyses to be considered. It needs only to be mentioned here that both Sir James Paget,[41] in 1853, and J. A. Korteweg,[42] in 1880, realized the limitations of early treatment and the reason for its failure. It should be mentioned, too, that Halsted, according to Lewis and Rienhoff,[16] was conscious of the need for re-appraisal of his radical mastectomy. But the number of analyses showing the limitations of treatment, early or otherwise, in more recent years has some significance in itself. Lewis and Rienhoff, 1932, not only recognized from their analysis of cases the limitations of microscopy, as noted, but also recognized the limitations of treatment. The surgeon, they said, could be responsible for the local lesion but not for the remote metastases which would eventually kill in the "large majority" of cases.[16] Grace, long cognizant of treatment failures that clashed with the premise on which treatment was based, sought the explanation and in 1937 concluded: "The cellular structure of the tumour is the dominant factor, and surgical technique, irrespective of the extent of its radicalism, plays a definitely secondary role."[43] Handley and Thackray's demonstration, in 1947, that about 60% of breast cancers with axillary metastases and a small percentage of those without axillary metastases show involve-

*It will be realized, of course, that the presently insuperable difficulties in diagnosis and differentiation are not the only factors making for dissimilarity in survival rates of series or parts of series differing in time or place. As many have emphasized, there is the difference in selection of cases for treatment or report after diagnosis, in staging criteria and in their application, in the detection of lymphatic involvement, in follow-up of cases and in calculation of survival rates.

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ment of the internal mammary lymphatics[44] (findings fully confirmed by Wyatt *et al.*[45]) exposed *one* of the fallacies of "cleaning out" the axilla as practised for 50 years in the belief that the disease might be thereby eradicated. Truscott, of the Middlesex Hospital, London, in 1947, after seeking for conclusive evidence of the value of treatment in an analysis of cases put his findings thus: "This investigation has forced one to the conclusion that no matter how early the case or thorough the treatment, no patient is free from the possibility of recurrence until death occurs from some other cause."[46] Bloom, in a clinical-pathological study of cases from the same hospital, in 1950, failed to find any regular decrease in survival rate with increasing pre-treatment duration, and after intensive investigation concluded: "We are compelled to adopt the view that outcome in mammary cancer is determined largely by the histological type of growth, rather than by prompt treatment as soon as the lesion is discerned."[15] In 1951, MacDonald, of the Department of Surgery, University of California, in a critical analysis of cases concludes: ". . . to no small extent the doctrine of synonymy of 'early' treatment and curability should be recognized for the shibboleth which it is."[26] Park and Lees, Edinburgh, 1951, in a clinical-pathological study, concluded: "(a) It has not been proved that the survival rate of cancer of the breast, using a five-year survival rate as an index, is affected by treatment at all. (b) The evidence strongly suggests that treatment is quite ineffectual in reducing the incidence of death from metastatic spread. (c) If treatment is in any way effective, the effectiveness cannot be greater than that required to increase the over-all five-year survival rate by more than 5 to 10%."[27] (The last item, (c), has been questioned by Gilliam,[47] who properly points out that its calculation involves an assumption and that different assumptions would give different estimates of curability and that the truth cannot be assured through calculations involving assumptions the validity of which cannot be assured.) Haagensen and Stout, 1951, as noted, while still apparently holding to early treatment, frankly present their later contrary findings: "Although in our 1915-34 series of cases the cure rate fell with the increasing duration of the disease as would be expected, the data in the present series [1935-42] do not show such a correlation. We are unable to explain this finding."[14] Smithers *et al.*, London, 1952, in their comprehensive survey conclude: "The most important factor in the prognosis in patients with breast cancer is the character of the tumours they develop."[48] In 1953, Williams, Murley and Curwen, in an analysis of 1,044 cases treated at St. Bartholomew's Hospital, report: "The most impressive finding in this series is the remarkable similarity in the survival rates following different methods of treatment. All the main treatment methods analysed [simple mastectomy or excision of the lump, modified radical mastectomy, radical mastectomy, each with and without irradiation, and irradiation alone] seem to have been equally effective in stages I and II. It must, however, be frankly recognized that all methods of treatment may have been equally ineffective in prolonging life."[28] Small and Dutton, 1955, in an analysis of about a thousand cases at the University of Rochester find that some patients with treated cancer die at normal rates, others at increased rates, ". . . that it appears that mortality in cancer is a constant process little affected by treatment" and ". . . it is doubtful if many more persons are cured by radical mastectomy than by other forms of treatment."[30] Even more recently George Crile, Jr., of the Cleveland Clinic Foundation, makes the summary statement, *inter alia:* "All evidence points to biologic predetermination and resistance of the host as the most important factors in the survival of patients with cancer of the breast."[49] And, in commenting on Crile's criticism of some radical surgery, Morris Fishbein says, ". . . this view is based on an honest recognition of our lack of knowledge or of certainty in distinguishing inoperable cancers from those that are operable. His forthright and independent statement will help to renew public confidence in surgical ethics."[50] Thus, the conclusions drawn from critical analyses of cases, as noted above, and also the considered statements of Crile and Fishbein are in practically full conformity with the deductions drawn from the nearly level trends in vital statistics and other relevant data.

OTHER CANCERS

Other cancers contributing relatively importantly to cancer mortality are far too subject to error and change in diagnosis, certification and bookkeeping for their official mortality records to serve as reliable bases for comparison. But,

prone to artefact though the figures of cancer by site are, the Ontario age-specific mortality rates for all cancer (combined) in the female have maintained fairly constant levels while those in the male have shown increases. Increases in pulmonary cancer largely account for the increases in the male rates, so that when the deaths charged to pulmonary cancer are deducted from the total cancer (combined) deaths, the general levels in the female rates are not much affected but the net rates in the male then hold to similarly persistent levels. The significance of these levels cannot be established as satisfactorily as in those of breast cancer. Nevertheless, they cannot be entirely disregarded. With 40-50% of cancer deaths in the female and only 5-10% in the male contributed by sites which are regarded as accessible, it would be expected that, if early treatment were effectual and if accessibility favoured early treatment, as it should, the rates in females would have fallen in relation to those in males. The fact that, apart from pulmonary cancer, they have not shown such displacement suggests that early treatment not only has failed in breast cancer (which makes up about 20% of cancer mortality in females) but that it has similarly failed in other cancers. Nor do the data for all cancer (combined) in females for England and Wales and Massachusetts, as previously examined,[8] provide any consistent evidence of appreciable control of that mortality. What of the contrary evidence?

Cervical cancer has usually been considered the other major cancer accessible for early diagnosis and treatment and therefore susceptible to control. Data of stage and duration of cervical cancer show that, as in breast cancer, stage is little related to duration; stage I includes all durations, short durations include all stages, and, when there is any difference between durations of stage I and other stages, it is relatively small.[51] Thus, as in breast cancer, stage is more an indication of type than of duration or developmental progress, and survival rates in stage I are fallacious evidence of the superiority of treatment of progressive cancer, either chronologically early or in an early developmental stage. Variations in diagnosis, differentiation, staging, follow-up of cases and calculation of survival rates in cervical cancer are fully as great as, if not greater than, in breast cancer. Thus, the higher survival rates in some series than in others differing in time or place are not reliable evidence of superiority of any difference in time or type of treatment. High survival rates have been reported for cervical carcinoma-in-situ and this lesion has even been classified in some series as stage 0 cancer. In a recent study Shier found that, of 50 cases of carcinoma-in-situ in which the observation period varied from one to 14 years with an average of four, with some of the cases (not associated with pregnancy) showing similar lesions on repeated biopsy over many months, with some treated for other conditions but none treated for cancer and 10 not treated in any way, none had progressed to invasive cancer; and in 10 not associated with pregnancy and not treated in any way the lesion disappeared spontaneously.[52] Thus, the survivals in carcinoma-in-situ, like the survivals in stage I cancer, are spurious evidence of survivals in early progressive cancer. Cannell has recently reported from an analysis of cases that removal of all accessible lymph-bearing tissue with vulval lesions does not give any assurance of cure.[53] While, therefore, the evidence in vital statistics regarding other cancers is not of the same quality as that for breast cancer, what there is is not conducive to any optimism, and other evidence that is so would appear to be as fallacious as that in breast cancer—and for the same reasons.

But it is as important to realize that in those cancers in which extension of the primary lesion with its complications may kill before remote metastases develop, such as many in the pelvis or abdomen and in some other sites, reasonably early treatment may materially prolong life even where it does not eventually prevent death. In non-metastasizing cancers, indistinguishable as they are in their architecture from metastasizing cancers, adequate early treatment can cure; but these cancers contribute only a small part of cancer mortality.

SUMMARY

Aggressive programmes over the past 25-30 years for the control of cancer mortality, and more particularly that of breast cancer, have failed to make any impression on the latter recorded mortality. That failure, considered with other pertinent data, requires the hypothesis that remote spread occurs before the lesion can be diagnosed and treated.

Consistent evidence shows that "stage I" does not mean "short duration" but is more suggestive

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of the *type* of breast cancer; it shows that microscopy does not reveal accurately the biological characteristics—the metastatic or lethal propensity—of a tumour, that "proven" microscopically does not necessarily signify a progressive lethal cancer but an architecture similar to or identical with that of progressive lethal cancer; and it shows that non-progressive lesions, unavoidably included as lethal cancer, make up a large part of most stage I cancers whether the latter form a large or a small part of a series. The wide variations in the survival time of patients with cancers of other stages also reflect wide variations in malignancy in these stages that are not accurately revealed by microscopy.

The evidence that treatment of breast cancer prevents death in a very considerable proportion of cases or that early treatment is greatly superior in this regard must be rejected because it is based for the most part on invalid comparisons of survival rates of series of cases the comparability of which was, in many instances, patently lacking and, in all, quite incapable of proof through microscopy; the differences in survival rates are reasonably attributable to differences in type of case rather than to differences in either time or type of treatment. Failure to take into account the present inability to differentiate accurately, through microscopy, between non-lethal and lethal cancers and between different degrees of malignancy in lethal cancers explains many of the inconsistencies and contradictions in breast cancer literature.

Findings from critical analyses in the clinical field are in full conformity with the hypothesis from the level trends in vital statistics of breast cancer. The value of local treatment of breast cancer cannot, therefore, be measured in lives saved but in the physical and mental relief it gives.

The evidence to date fails to give assurance that material reduction of deaths from any metastasizing cancer has yet been achieved. The high survival rates reported for early treatment of cervical cancer and the like are attributable to misconceptions and presently insuperable difficulties in diagnosis and differentiation similar to those found in regard to breast cancer.

In metastasizing cancers that kill through local extension and its complications before remote metastases cause trouble, adequate local treatment can postpone death. In non-metastasizing cancers, such as most skin cancers or what are called cancers, adequate local treatment can cure; but non-metastasizing cancer accounts for only a small part of cancer mortality.

As cancer data are unavoidably lacking in complete accuracy and no measurements of its mortality can be precise, the possibility that death may be prevented in an occasional case of breast or other metastasizing cancer by early or extensive treatment cannot be denied; but, if any, the number of such cases is too small to make any decisive impression on the recorded rates.

ADDENDUM

Since the above manuscript was submitted there has come to hand an analysis of *The Problem of Prognosis in Cancer of the Breast* by Edward F. Lewison, of the Breast Clinic Division of the Tumour Clinic, Johns Hopkins Hospital and Johns Hopkins University (*Surgery*, 37: 479, 1955). Even at the risk of giving a wrong impression of Dr. Lewison's views, a risk which might be obviated by this caution, the following excerpts are taken out of their context:

. . . "Each factor of prognosis is merely a straw in a wistful wind." . . .

. . . "Thus, prognosis is unpredictable, and cancer today gives no sure measure of cure tomorrow."

"With true humility we must confess that despite prompt and adequate treatment, we do not know precisely which individual patient will be favoured by fortune and granted a long survival. Certainly the cardinal concept of early diagnosis and early treatment well done cannot help but contribute toward this hope and expectation."

"While some of these factors may be related to the alertness and understanding of the patient and the diligence and initiative of the physician, as stated by Smithers and co-workers, prognosis 'is largely dependent on the rate of growth and tendency to dissemination of the tumour'."

"In the dilemma of prognosis, currents and cross currents of biologic behaviour flow beneath the surface of unpredictable clinical speculation. The measure of these forces and their influence on survival cannot as yet be calculated with exactitude."

And in a study, *Latent Carcinoma* (*Ann. Royal Coll. Surg.*, 15: 236, 1954), L. M. Franks, of the Imperial Cancer Research Fund Laboratories, says, in summary: "If certain organs, particularly the prostate, lung, kidney, thyroid and perhaps stomach, are carefully examined, large or small carcinomas can be found in them with remarkable frequency. One can reasonably expect to find an occasional small tumour by chance in any organ but the fact that these tumours are found in such a high proportion of cases must mean that their development is retarded. The tumours are latent tumours. Why they remain latent we do not know and we can only speculate on their significance. The answers to these problems seem to me to be of some importance."

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RÉSUMÉ

Depuis 25 ou 30 ans, d'ambitieux programmes pour enrayer la mortalité par le cancer, et particulièrement par le cancer du sein, n'ont pas réussi à diminuer les statistiques de mortalité de ce dernier. Cet échec, ajouté à d'autres données sur le sujet, nous porte à émettre l'hypothèse que l'envahissement éloigné a lieu avant que la maladie ne puisse être traitée ou même diagnostiquée.

Des preuves solides démontrent que: (1) "le premier stage" n'a rien à voir avec la durée de la lésion, mais il désigne plutôt le type de cancer du sein; (2) que l'examen microscopique ne révèle pas toujours exactement les caractères biologiques d'une tumeur, à savoir: sa capacité de produire des métastases et de causer la mort; (3) que "vérifié au microscope" ne signifie pas nécessairement un cancer en évolution, mais bien une structure semblable ou identique à celle d'un cancer en évolution; (4) enfin, que des tumeurs qui n'évoluent pas, incluses inévitablement dans les tumeurs malignes, forment une grande partie de la plupart des cancers du premier stage, dans toute série. Les grandes variations dans la survie des malades atteintes de cancer aux autres stages démontrent aussi de grandes variations dans la malignité à ces stages qu'on ne peut évaluer clairement au microscope.

L'opinion que le traitement du cancer du sein empêche la mort dans une proportion considérable des cas ou qu'un traitement précoce est recommandable, doit être rejetée parce qu'elle est basée surtout sur des comparaisons boiteuses de survie dans des séries de cas qui ne pouvaient se comparer entre eux, et, dans l'ensemble, impossibles à vérifier au microscope; les différences de durées dans la survie sont attribuables, avec raison, aux différences de types de cancers plus qu'aux différences dans le genre ou l'époque du traitement.

Beaucoup d'inconséquences et de contradictions au sujet du cancer du sein tiennent au fait qu'on oublie l'impuissance actuelle à différencier les unes des autres exactement au microscope les tumeurs malignes et les tumeurs bénignes, de même que les différents degrés de malignité des cancers fatals.

Les données de l'analyse en clinique correspondent exactement à l'hypothèse inspirée par le niveau des statistiques de survie du cancer du sein. La valeur du traitement local du cancer du sein ne peut donc pas s'estimer d'après le nombre de vies sauvées mais par le soulagement physique et mental qu'il procure.

Nous n'avons pas de preuve jusqu'à présent qu'une diminution des décès cancers métastiques ait été réalisée. Le taux élevé de survie qu'on nous présente comme résultant du traitement précoce du cancer du col et autres provient de malentendus, de conceptions erronées, et de difficultés actuellement insurmontables dans le diagnostic et la différenciation, comme pour le cancer du sein.

Dans les cas de cancers métastatiques où la mort survient par un envahissement local et ses complications, avant que des métastases éloignées ne soient en jeu, un traitement local approprié peut retarder la mort. Dans les cancers non métastatiques, comme la plupart des cancers de la peau—ou ce que l'on nomme cancer—un traitement local approprié peut guérir; mais les cancers non métastatiques comptent peu dans la mortalité par le cancer.

Comme les données sur le cancer sont inévitablement inexactes et qu'on ne peut connaître le taux précis de mortalité, on ne peut nier la possibilité de survie dans quelques cas isolés de cancer du sein ou autres cancers métastatiques grâce à un traitement précoce et radical; mais ces cas, s'il y en a, sont si rares qu'ils ne peuvent avoir une influence décisive sur les statistiques.

M.R.D.

THE EDUCATED MAN IN 1955

"Nobody in 1955 can ignore scientific thinking and its consequences.

Many people brought up in the 'humanist' tradition not only do not know many scientific facts which are important; but also, more fundamentally, are incapable of certain modes of thinking derived from scientific studies and indispensable to an understanding of affairs in 1955. This does not mean that the scientist is automatically a more educated man than the non-scientist; he may be illiterate, incapable of historical imagination or of human insight. But it does mean that there are people who are scientifically illiterate. Nor does it mean that the scientist is the man who should decide politics—local, national or international. That is a misunderstanding of the nature of his training and his skills, especially as he must often, for the purpose of his own studies, ignore human factors."—*Nature*, 176: 466, 1955.

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MORTALITY TRENDS IN CANADA FOR VARIOUS SITES OF CANCER

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THIS PAPER presents an analysis by sexes of the deaths in Canada‡ assigned to nine of the major sites of cancer and to leukæmia. The sites and conditions which have been selected for study with their respective International List (Detailed) numbers are:

Buccal cavity	140-148
Stomach	151
Intestines	152-153
Rectum	154
Respiratory system	161-163
Urinary organs	180-181
Breast (female)	170
Uterus	171-174
Male genital organs	177-179
Leukæmia and aleukæmia	204

The period under review covers the years 1941 to 1953 inclusive. The year 1941 was chosen as a suitable starting point since deaths assigned to certain sites of cancer such as stomach and intestines were not listed separately in the annual Vital Statistics reports for Canada before that year.

The statistical procedures which have been used in analysis of the data may be explained briefly as follows. First, all mortality rates were age-adjusted to the Canada 1951 census population as a standard. The purpose of the age-adjustment or standardization procedure is to account for changes in rates which are due to changes in the age structure of a population in the course of time. Since cancer death rates increase greatly with age, and since the population of Canada is aging—that is, the relative number of older individuals is increasing—it is essential that this age-adjustment be carried out whenever any comparison of rates in time is made.

Second, the trend line for each set of age-adjusted rates was found. This line is, among all possible lines, the one for which the sum of the squared vertical distances from it to the points representing the rates is a minimum. It is commonly known as the "best-fitting" line. If as we proceed through the time interval under consideration (1941-1953) this line tends to rise, it has a positive slope. If the line falls the slope is negative, and if it is horizontal the slope is zero. When the line has a positive or negative slope, it signifies that the rates have increased or decreased during the interval and we compute the probability that a true rise or drop has occurred. This probability depends on two things: the magnitude of the slope of the line, and the amount of scatter of the actual points about the line.

In each of the analyses the probability value of less than 0.05 was considered sufficiently small to call a slope significantly different from zero. Hence, a "significant" trend indicates that the probability of obtaining, through chance alone, a set of rates which would give rise to this trend, or one at least as pronounced, is less than 5 in 100.

In this study it will be noted that the actual death rates for some sites are increasing or decreasing, but the subsequent tests for significance show that the increase or decrease may be due to chance variation. This indicates the weakness of interpreting mortality trends from an inspection of age-adjusted death rates and points out the necessity for testing for significance.

ANALYSES OF SPECIFIC SITES OF CANCER

The age-adjusted mortality rates for the nine sites of cancer and for leukæmia are shown for males in Table I and for females in Table II.

BUCCAL CAVITY AND PHARYNX

This analysis includes those deaths attributed to cancer of the lip, tongue, salivary gland, floor of mouth, other parts of mouth, oral mesopharynx, nasopharynx, hypopharynx and pharynx (unspecified). The trend lines for mortality from cancer at these sites are shown for males and females in Fig. 1. The slopes of these lines show that in males there has been a significant decrease in mortality. The male death rate has dropped 34.7% between the years 1941 and 1953.

STOMACH

The trend lines for mortality from cancer of the stomach are shown for males and females in Fig. 2. Each of these lines reflects a significant

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‡A more comprehensive report including analyses for each of the provinces has been prepared and may be obtained upon request to the National Cancer Institute of Canada, 800 Bay Street, Toronto.

TABLE I.

AGE-ADJUSTED MORTALITY RATES PER 100,000 POPULATION IN CANADA*
FOR VARIOUS SITES OF CANCER—MALE

Year	*Buccal cavity*	*Stomach*	*Intestines*	*Rectum*	*Respiratory system*	*Urinary organs*	*Genital system*	*Leukæmia*
1941.....	7.2	31.7	15.0	7.1	9.1	7.4	12.9	3.8
1942.....	7.0	30.9	15.2	7.4	8.9	7.6	12.4	3.6
1943.....	7.1	30.9	15.6	7.5	9.9	7.8	12.6	3.9
1944.....	6.5	29.9	14.8	8.5	9.8	7.7	12.1	4.2
1945.....	6.1	30.2	15.6	7.8	10.4	7.7	11.9	4.0
1946.....	5.7	28.2	14.9	7.5	11.9	8.0	12.5	4.3
1947.....	5.9	29.0	15.2	7.9	13.3	8.1	13.5	4.8
1948.....	6.1	27.9	14.9	8.3	13.9	8.5	13.3	4.7
1949.....	5.9	27.5	14.9	7.8	15.6	8.1	14.1	4.9
1950.....	5.4	26.6	14.6	8.2	16.5	8.4	14.1	4.8
1951.....	4.9	27.2	14.0	7.0	17.3	8.4	13.4	5.2
1952.....	4.9	28.0	16.0	7.2	19.2	8.2	14.4	5.3
1953.....	4.7	25.4	14.9	8.0	20.4	8.3	14.5	6.3

*Excluding Newfoundland.

TABLE II.

AGE-ADJUSTED MORTALITY RATES PER 100,000 POPULATION IN CANADA*
FOR VARIOUS SITES OF CANCER—FEMALE

Year	*Buccal cavity*	*Stomach*	*Intestines*	*Rectum*	*Respiratory system*	*Urinary organs*	*Breast*	*Cervix† uteri*	*Corpus† uteri*	*Leukæmia*
1941.....	1.4	18.1	17.8	5.1	3.2	3.9	22.7	7.9	9.7	2.9
1942.....	1.7	17.9	18.1	5.1	3.1	4.2	22.5	7.1	11.3	3.0
1943.....	1.6	17.9	18.3	5.4	3.6	4.0	23.4	6.5	10.8	2.6
1944.....	1.4	16.8	19.8	5.3	3.9	4.3	22.1	7.0	10.4	3.4
1945.....	1.3	15.3	19.0	5.1	3.4	4.1	22.7	8.0	9.9	3.0
1946.....	1.2	16.8	18.9	5.2	3.4	3.9	23.3	6.9	10.2	3.5
1947.....	1.3	14.9	18.4	5.5	4.8	4.3	22.4	7.8	9.6	3.3
1948.....	1.3	16.1	18.7	5.5	3.7	4.1	23.5	7.6	9.0	3.4
1949.....	1.3	14.6	17.2	5.1	4.4	4.4	22.7	7.9	8.3	4.3
1950.....	1.2	14.3	18.0	4.8	3.3	4.6	22.9	8.0	7.3	4.5
1951.....	1.3	13.8	18.5	5.6	3.7	4.1	22.9	9.0	7.4	3.9
1952.....	1.3	14.0	17.8	5.2	4.0	4.0	23.2	8.7	6.7	3.9
1953.....	1.4	14.1	17.3	5.0	3.6	3.9	24.1	8.1	5.9	4.1

*Excluding Newfoundland.
†These rates are added to give the rate for uterus including cervix.

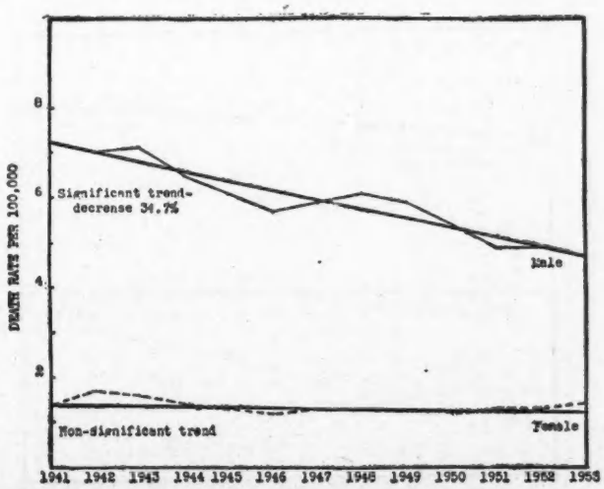

Fig. 1.—Mortality trends in Canada for cancer of the buccal cavity and pharynx.

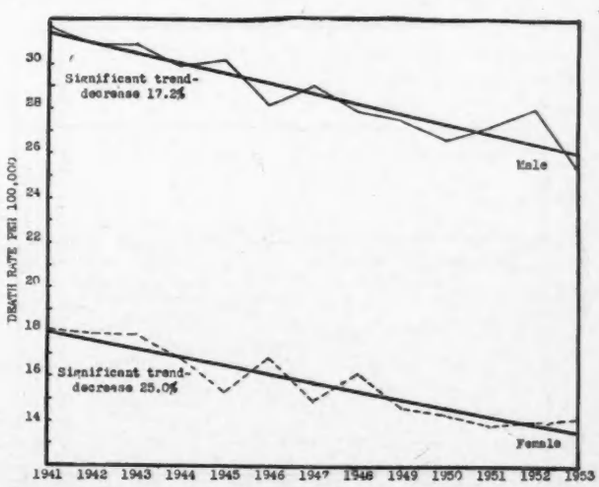

Fig. 2.—Mortality trends in Canada for cancer of the stomach.

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decline in mortality. Over the period 1941 to 1953 the male death rate has dropped 17.2% and the female 25.0%.

INTESTINES

The trend lines for mortality from cancer of the intestines are shown in Fig. 3. It will be noted that the age-adjusted mortality rates for females are consistently higher than those for males throughout the period. The slopes of the trend lines show no significant change in either male or female mortality.

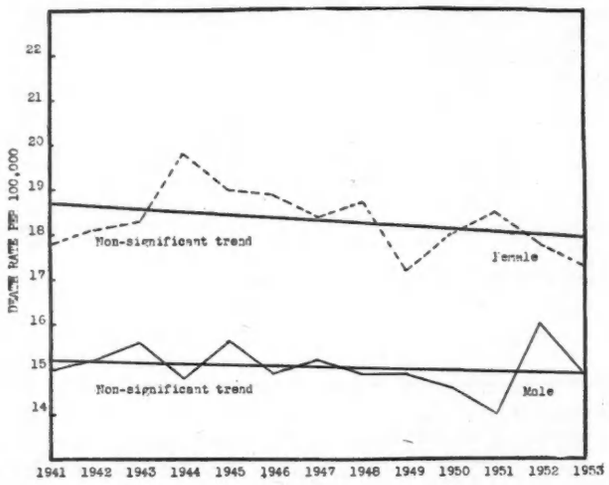

Fig. 3.—Mortality trends in Canada for cancer of the intestines.

RECTUM

The analysis of the deaths ascribed to cancer of the rectum, shown in Fig. 4, indicates no significant change in either male or female mortality.

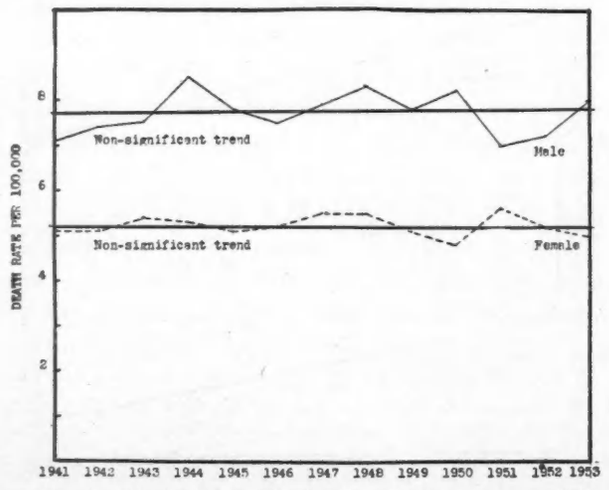

Fig. 4.—Mortality trends in Canada for cancer of the rectum.

RESPIRATORY SYSTEM

This analysis includes those deaths attributed to cancer of the larynx, trachea, bronchus and lung. The trends are shown in Fig. 5. The exponential curve has been used to represent the trend in male mortality since it fitted the rates more closely. There has been a significant increase in the death rates among males but no significant change among females. In males the age-adjusted death rate has increased 141.7% over the years 1941 to 1953.

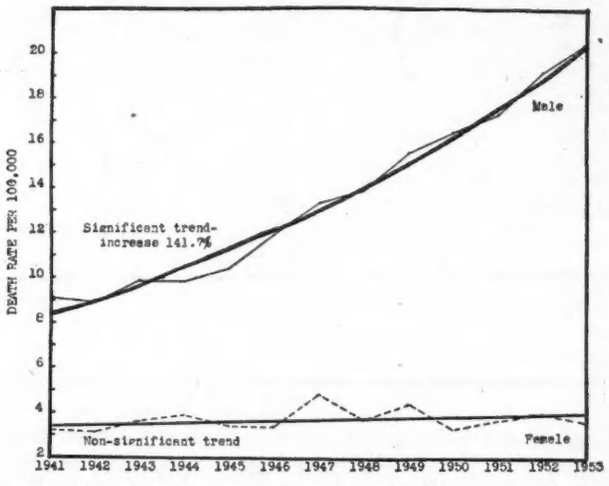

Fig. 5.—Mortality trends in Canada for cancer of the respiratory system.

URINARY ORGANS

The analysis of the deaths attributed to cancer of the urinary organs is shown in Fig. 6. The slopes of the trend lines indicate that, over the period 1941-1953, a significant increase in mortality has occurred in males but no significant

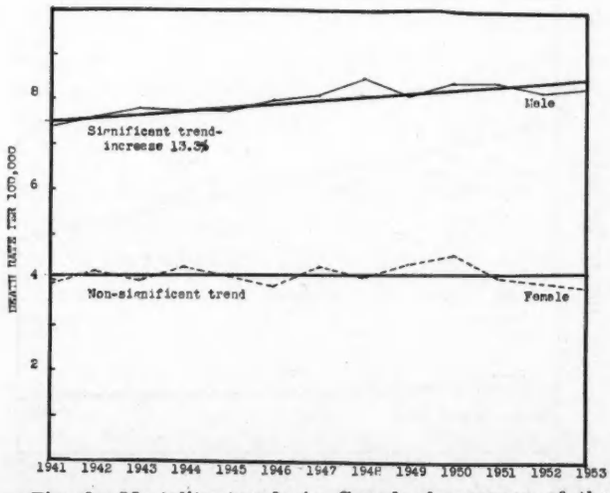

Fig. 6.—Mortality trends in Canada for cancer of the urinary organs.

change has occurred in females. In males the age-adjusted death rate has increased 13.3%.

BREAST

The analysis of the deaths attributed to cancer of the breast in females, shown in Fig. 7, indicates that no significant change in mortality has occurred over the years 1941-1953.

UTERUS

Two analyses have been made of the deaths attributed to cancer of the uterus, as shown in Fig. 8. In the first, deaths from cancer of the cervix uteri have been considered separately from cancer of the corpus uteri and other parts of the uterus; in the second they have been included. The slopes of the trend lines indicate a significant increase in recorded mortality for cervical cancer and a significant decrease for other parts of the uterus. The age-adjusted death rate for deaths from cancer of the cervix increased 21.4% while that for other parts of the uterus decreased 42.1%. However, the age-adjusted death rates for cancer of the uterus including the cervix decreased significantly, showing a drop of 17.9%.

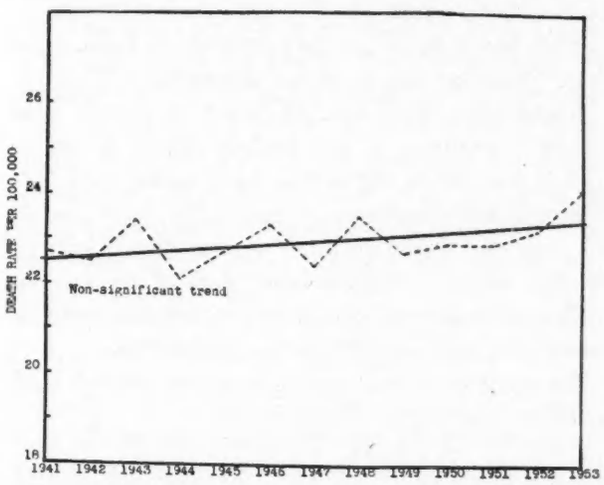

Fig. 7.—Mortality trend in Canada for cancer of the female breast.

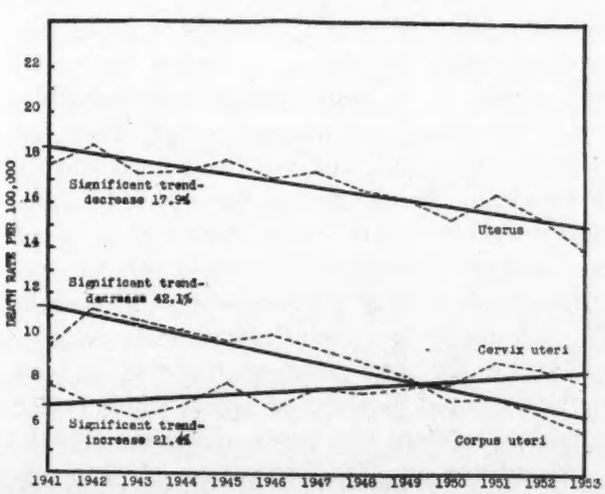

Fig. 8.—Mortality trends in Canada for cancer of the uterus.

MALE GENITAL ORGANS

This analysis includes those deaths attributed to cancer of the prostate, testis and other male genital organs. The slope of the trend line, shown in Fig. 9, indicates that a significant increase in mortality rates has occurred over the period being studied. This increase amounted to 19.8%.

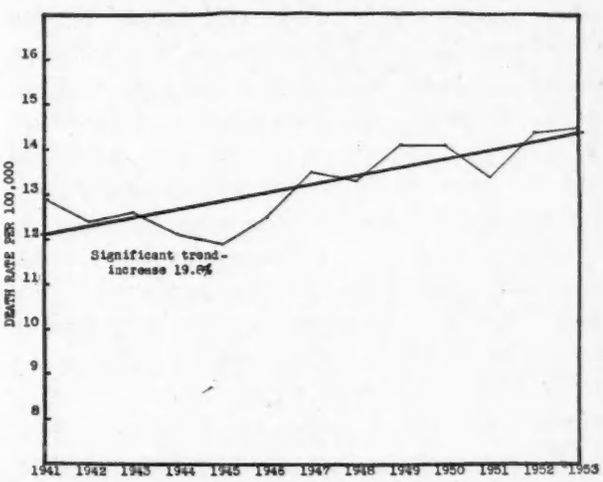

Fig. 9.—Mortality trend in Canada for cancer of the male genital organs.

LEUKÆMIA AND ALEUKÆMIA

The analysis of the deaths attributed to leukæmia and aleukæmia is shown in Fig. 10.

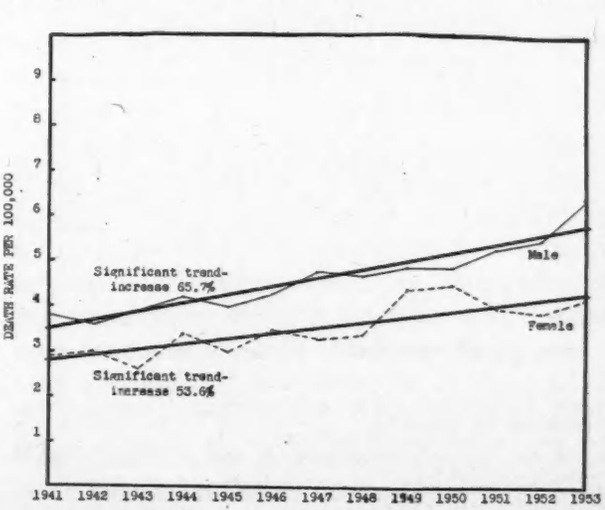

Fig. 10.—Mortality trends in Canada for leukæmia.

Deaths from Hodgkin's disease are not included in the analysis. The slopes of the trend lines indicate that a significant increase in mortality has occurred in each sex. The age-adjusted death rate has increased 65.7% in males and 53.6% in females.

DISCUSSION

A study of trends in recorded mortality is a study of three variables: biological phenomenon, medical opinion and the method of selecting the primary cause of death from the death certificate. In the present study the last of these has been made constant by means of the comparability ratios which were calculated by the Dominion Bureau of Statistics on the deaths in Canada in 1949. In that year the sixth revision of the International Classification of Diseases, Injuries and Causes of Death was published and, in order to assess the variations between this revision and the previous one, all deaths in Canada in 1949 were tabulated by both. From this dual tabulation the comparability ratios were calculated. These ratios have been used in the present analysis of the mortality data for the years 1941-1949, hence these data are directly comparable with those for the years 1950-1953.

Of the remaining two variables, the biological phenomenon and the medical opinion, it is impossible, from the data available, to separate the contribution of each to the trends. In certain sites there probably is reason to believe that the trend is influenced more by one variable than by the other. For example, in deaths from cancer of the uterus and cervix, the inverse trends are very likely due to more precise medical identification of the site of origin of the disease. On the other hand, one would hesitate to ascribe the decrease in deaths from cancer of the stomach entirely to the variable of medical opinion.

SUMMARY

A statistical analysis by sexes has been made of the recorded deaths in Canada attributed to cancer at nine sites and to leukæmia during the period 1941-1953. The trends in the age-adjusted death rates for each site and sex have been tested for significant increases or decreases by means of Student's *t* test.

Significant decreases in mortality in both sexes were found in cancer of the stomach.

Significant decreases in mortality were also found in cancer of the buccal cavity in males and in cancer of the uterus in females.

Significant increases in mortality were found in cancer of the respiratory system and in cancer of the urinary organs and genital organs in males, in cancer of the cervix in females, and in leukæmia and aleukæmia in both sexes.

No significant changes in mortality were found in the following sites and sexes:

Buccal cavity	females
Intestines	males or females
Rectum	males or females
Respiratory system	females
Urinary organs	females
Breast	females

The authors wish to acknowledge the assistance of the Dominion Bureau of Statistics in this study.

OBSERVATIONS ON THE PATHOGENESIS OF NEOPLASIA*

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IN CONTRAST to many previous theories of cancer, recent experimental observations suggest a concept of neoplastic diseases which is more closely related to clinical experience in human neoplasia. For decades the opinion was held that cancer is an autonomous, uncontrollable, self-perpetuating, independent entity. Thus the main emphasis was not on the natural history of neoplastic disease but on the search for etiological agents. There were several theories of the etiology of neoplasia, but they left the description of further development of cancer in the darkness of "autonomy". More confusion was added by the accumulating evidence of the multiplicity and diversity of agents which under suitable conditions may cause malignant growth.

In addition to the observation of "cancerigenesis without cancerigen" and the evidence

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that simple prolonged deviation in physiological function of some organs may give rise to neoplasia, other important facts contributed to limit the validity of the concept of neoplastic diseases based on "autonomy". It has been shown that the process of cancerization is fundamentally developmental in nature, that so-called "cancer cells" may remain in the body for indefinite periods without giving rise to clinically perceptible cancer, that some malignant tumours are dependent on intrinsic biological factors for their growth and progression, and finally that even metastatic growth on rare occasions appears to be under biological control and may eventually regress. This seems to indicate that tumour and host form an inseparable, interacting biological unit. The recent trend in the investigation of various aspects of neoplastic diseases shifts the emphasis from etiology to pathophysiology. The purpose of this paper is to analyze the pertinent observations and to correlate them with our experience in experimental carcinogenesis.

MALIGNANT CHARACTERISTICS

In view of various terms applied in description of the neoplastic process, it appears necessary to define certain basic terminology, which will be followed in further discussion. The first question concerns the use of the term "carcinogen", which is commonly understood to mean "agent inducing cancer". This term does not convey the interplay of factors, frequently non-carcinogenic themselves, which is necessary to initiate malignancy. It should also be remembered that certain conditions of tumour induction, such as the spontaneous malignant changes of tissues *in vitro*, do not necessitate the use of any known carcinogens. Therefore the term "inducing agents" will be used with reference to carcinogens. By "co-ordination of inducing agents" is understood a combination of various factors which are interdependent in their ability to induce the specific biological condition of malignancy.

The "malignant characteristics" represent descriptive entities, the summation of which constitutes the distinctive character of malignancy. Malignant characteristics result from action of inducing agents and have to be present in certain combinations to be regarded as pathognomonic of cancer. None of them, when occurring alone, is characteristic of the neoplastic process, as similar characteristics can be found in normal tissue constituents. For instance, the invasion of cancer cells can be compared with the ability of certain normal cells to migrate, penetrate the tissues and remain there. Neither can perpetuity of growth be considered as limited to neoplasia; it can be found in normal growth of rodents' teeth. It is interesting to note that normal tissues cultivated *in vitro* tend to form marginal metastases and show a decrease in the degree of differentiation. Malignant characteristics can be divided into latent and manifest. Latent malignant characteristics are synonymous with "malignant potentialities". To illustrate the difference the following example may be given: Ability to invade the tissues and ability to metastasize represent malignant potentialities, while the process of invasion or development of metastases represents a manifest malignant characteristic.

The following malignant characteristics are generally recognized: (1) growth; (2) heterotopia; (3) anaplasia. To these might be added: (4) relative unresponsiveness to extrinsic stimuli; and (5) the faculty to elicit local and systemic reactions in the autologous host.

The faculty of growth. — By the term *growth*, as a distinct malignant characteristic, is understood a simple increase in mass. The growth rate in all stages of neoplasia depends on two factors: (1) the inherent growth momentum of the cell; (2) the degree of responsiveness to extrinsic stimuli. The increased growth rate of malignant tissue does not seem to be as characteristic of the process as the permanence of growth. Several examples of growth in normal tissues proceeding at a higher rate than in neoplasia can be quoted. The permanent character of growth is apparent in the majority of malignant tumours. However, the tumour may cease to grow permanently or temporarily.

The faculty of heterotopia.—The term "heterotopia" includes several distinct malignant characteristics: invasion, formation of metastases, and transplantability. Ability to form metastases can be further subdivided into the faculty to detach from the bulk, to migrate, and to grow in abnormal locations. The last-mentioned represents actually the part played by heterotopia in formation of metastases. Homotransplantability appears not to be a characteristic property of neoplastic tissue, as commonly believed. Heterotransplantability, according to Greene, signifies

the fact that the neoplastic process has reached a stage of "autonomy". This term corresponds to the ultimate phase in our classification outlined in the course of this paper. The possibility has been pointed out that many tumours believed today to be autonomous may be dependent on unknown factors.

The faculty of anaplasia represents a morphological entity, which according to definition signifies a process by which the cells in question lose partially or totally their distinctive character. The loss of characteristics which distinguish the cells as specific is typical. Anaplasia is manifested morphologically by loss of orderly histogenesis, biochemically by simplification of chemical composition, or physiologically by complete or partial loss of normal function.

The faculty of relative unresponsiveness to extrinsic stimuli.—That this property is a relative one should be emphasized because of increasing evidence that many tumours respond to extrinsic stimuli of wide variety. Failure to respond to extrinsic influences may concern one or several malignant characteristics; in other words, it may be separately distributed as to various characteristics. For instance, growth of a thyroid carcinoma might be regulated by the level of thyroid-stimulating hormone of the pituitary and the growth rate might correspond to the secretory level of TSH, whereas the ability to form metastases might remain unaffected. Therefore it appears necessary to specify which of the malignant characteristics is in the unresponsive state, i.e. in a state of autonomy.

The faculty to elicit local and systemic reactions in the autologous host.—This represents a definite group of malignant characteristics, though relatively little is known about the reactions of the autologous host to the presence of a tumour. The following reactions elicited by the tumour in the autologous host may be mentioned: (1) faculty to evoke excessive connective tissue reaction, as evident in the formation of tumour stroma; (2) faculty to induce formation of new blood vessels; (3) faculty to compete effectively with normal cells for nutrition; (4) faculty to evoke immune reactions in the autologous host.

PROGRESSION IN NEOPLASIA

As observed in embryology, normal development progresses towards a predetermined point. The quantitative and qualitative progression in malignant characteristics does not seem to have such final delineation. The property of unlimited progression appears to be one of the most distinctive faculties of neoplastic tissues. During this process the tissue in question increasingly loses the characteristics of normal tissues. It should be emphasized that increase in malignant potentialities does not necessarily signify an increase in manifest malignant characteristics; ability to invade the surrounding tissues might increase progressively over a period of time without being manifest as an actual invasion. The progression in malignant characteristics may concern only one faculty, such as invasiveness, without necessarily affecting other characteristics, such as formation of metastases or degree of responsiveness to extrinsic stimuli.

It is apparent from previous discussion that the ultimate phase of neoplasia is a result of progression in malignant characteristics, the neoplastic tissue achieving a state of "autonomy" or "independence from extrinsic influences". This progression toward final insusceptibility to influences is not, however, an exclusive characteristic of malignancy. The acquisition of new characters is a common faculty of living matter and progressive autonomization is a common property of all living systems. Weiss[27] has stated that "any sequence of protoplasmic transformations that greatly outlasts the duration of the condition that set it off, will give the appearance of an autonomous intrinsic change." Thus malignant cells are not unique in their ever-increasing autonomy.

Progression in malignant characteristics may cease temporarily or, as recent observations indicate, even permanently. It may result in complete regression of the tumour, as shown in some human neoplasms such as chorionepitheliomas, juvenile papillomas of the larynx and neurogenic tumours in infants.[6] Similarly, some tumours cultivated in chick chorio-allantoic membranes may recover antecedent, less malignant characteristics. It remains for further investigation to establish how far these results bear on the problem of reversion of the malignant process. It appears that progression may lead to any intermediate between the two possibilities: ultimate (independency) phase of malignancy or complete regression of the tumour. Needless to say, the "autonomous" phase is the most frequently observed sequel of progression.

Some factors responsible for progression in manifest malignant characteristics are now known. The classical work of Gardner[9] on the effects of œstrogens on latent mammary cancer cells has demonstrated them in a particularly understandable way. However, there is almost complete ignorance concerning the nature of the progression in malignant potentialities and the factors affecting its direction. Such factors might possibly be recognizable clinically or biochemically.

DEVELOPMENTAL CHARACTER OF MALIGNANCY

Early workers in experimental carcinogenesis regarded malignant change as a one-step cause-and-effect event. In later studies the developmental character of malignant growth has been increasingly recognized, as shown in the investigations of Rous and Kidd,[21] Berenblum,[2] Green[10] and Mottram.[18] Rous drew attention to the subthreshold neoplastic states, which under adequate stimulation give rise to benign and malignant tumours. In experimental work with polycyclic hydrocarbons, progressive acquisition of neoplastic characters has been observed. Conclusive evidence came, however, from experience in induction of neoplasia with various hormones. In most tumours induced by hormonal stimulation, the step-like development of malignancy from hyperplasia or dysplasia through benign neoplasia is apparent. Clinical observations show that similar evolution of malignancy can frequently be followed, especially in intestinal, vesical and uterine tumours. The long interval between exposure to industrial carcinogenic agents and the appearance of clinical cancer similarly suggests the existence of a developmental process in human malignancy.

These observations formed the basis for the original suggestion of Rous[20] that "tumours develop by progressive acquisition of permanent new characters". Kline and Rusch[16] distinguished in 1944 three phases in the neoplastic process: (1) a period of induction, during which the neoplastic cell is formed; (2) a critical period, corresponding to a transitional state in which the neoplastic cells are in equilibrium with their environment and growth depends on the balance between the proliferative capacity of the cell and the local tissue resistance; (3) a period of progression, during which the growth is relatively unchecked. In 1950 Greene[11] divided tumours into "dependent" and "autonomous", on the basis of behaviour of anterior eye chamber transplants. According to Greene,[11] at the stage of dependence the survival of cancer cells depends on the constitutional status of the tumour-bearing individual. "Autonomy" signifies the fact that tumour becomes independent of these factors and that it will survive in their absence. Furth[8] suggested the division of neoplasms into "conditioned" and "autonomous". Because of the obvious difficulty of integration of the nomenclature of Greene and of Furth into the original classification of Kline and Rusch, we have suggested division of the neoplastic process into the following phases: (1) The induction phase, during which neoplastic change in the tissue takes place. This period includes the genesis of neoplastic potentialities which may be manifest or remain latent. (2) The critical phase, during which further development of tumours depends on the action of promoting and inhibitory factors. This period includes the "dependent" and "conditional" neoplasms of Greene and Furth. The difference in definition of this phase and the critical phase of Kline and Rusch lies in the fact that the latter authors regarded the phase as a strictly local event, not including the possibility of tumour dependence on extrinsic (i.e. extra-tumoural) factors. (3) The ultimate phase, during which the neoplastic process becomes "autonomous" and therefore theoretically independent of any extrinsic influences. In other words, in the ultimate phase the proliferation of tumour cells is not restricted by the usual regulating mechanisms. In the ultimate phase, under certain conditions, the organism may achieve control of the neoplastic process by more or less "unusual" regulating mechanisms. The use of the term "progression" was avoided with reference to this phase, since progression in malignancy constitutes a process not restricted to the phase of independent growth.

THE INDUCTION PHASE

During this phase a "carcinogenic" agent, frequently of known nature, brings about a neoplastic change in the cells under mostly unknown environmental conditions. The intimate mechanism by which this change occurs is at present obscure. In descriptive terms, the neoplastic change in the cell signifies the fact that the tissue

has acquired the ability to progress in malignant characteristics.

As has been mentioned previously, the number and variety of known carcinogenic substances is constantly increasing. Cancer may be induced by such diverse agents or conditions as polycyclic hydrocarbons, mechanical pressure, fats, nutritional deficiencies, viruses, and repeated transplantation of normal tissues or by mere cultivation of tissues *in vitro*. It is therefore apparent that everyone is exposed repeatedly to numerous cancer-inducing agents and conditions, and conceivably the cancerization of some cells is inevitable during the life span. The importance of susceptibility of tissues should be recognized as a basic factor in tumour-induction, in addition to the fact of exposure to some inducing agent. Local carcinogenesis may be considered as a "field response" in which the fate of a given cell is determined by the position of an element within a group, and dependent on the environmental condition of the cells, resulting from action of a variety of integrated factors. When added to the diet remote chemical carcinogens, such as 2-acetylaminofluorene, induce tumours in various tissues such as liver, lungs, sebaceous glands, intestines and urinary tract. The site and incidence of the tumours depend on the strain of the animals used and various localizing factors.[22] Even in a single inbred strain, the site and frequency of tumours vary greatly. The host susceptibility or resistance appears to be a factor of as great importance as the sole fact of exposure to an inducing agent. One may recall here the dictum of Claude Bernard in his "Introduction to the Study of Experimental Medicine".[3] In 1878, he wrote: "External influences bring about changes and disturbances in organic functions only in so far as the protective system of the organism's internal environment becomes insufficient in given conditions." This thesis seems to have full validity in respect to experimental carcinogenesis. The body has the ability to maintain an unchangeable cellular environment by complex cellular, tissular and systemic homœostasis. An interplay of factors breaking down this mechanism in a particular way seems necessary for the development of a malignant change.

The current state of knowledge recognizes basically two processes by which a cell can acquire new and hereditary characters: (1) somatic mutation, and (2) infection by exogenous viruses or endogenous plasmagens. By combination of some components of both processes, the following mechanisms of cancerization have been postulated: (1) Inducing agents such as polycyclic hydrocarbons or irradiation cause somatic mutation of the cells, leading to formation of so-called cancer cells. (2) Inducing agents merely sensitize the tissues to the action of other (exogenous or endogenous) mutagenic agents. (3) Inducing agents change a particular cytoplasmic component, which is transmissible to daughter cells, and thus act similarly to an endogenous virus; this is known as the plasmagene theory of cancer. (4) Inducing agents facilitate the action of exogenous viruses on the cells (the exogenous virus theory). (5) Inducing agents modify the environment in a way which favours the survival of malignant cells, previously developed by spontaneous somatic mutation; this is known as the theory of selective cancerization.

Mutation is generally conceived as a sudden and relatively permanent chromosomal change. It is characterized by a change in the individual genes (gene mutation) or by a structural aberration of chromosomes (inversion, translocation) or by changes in numbers of whole chromosomes per nucleus (e.g. polyploidy). Somatic mutation may occur in a somatic cell spontaneously and then be transmitted to all cells derived by mitosis from that cell. Since Boveri's suggestion in 1904, the opinion has been held that in all tissue cells of an individual a constant number of chromosomes is present. It was thought that the continuity of normal cell behaviour was assured by rigid maintenance of integrity of the chromosomal apparatus. Abnormal chromosomal combinations were believed to lead to abnormal cell characters and among other possibilities to cancer. This view formed the basis for tumour origin postulated by Boveri,[4] the abnormality being recognized as mitotic and heteroploid variability. However, recent investigations have questioned the validity of this hypothesis. It has been found that mitotic abnormalities and widespread heteroploidy are universal phenomena in normal embryonic and adult tissues. It was observed by Timonen[26] that the number of chromosomes in human endometrium varies between 4 and 104. The mitotic irregularities found in normal endometrium are qualitatively similar, though less frequent than in malignant tissues. The question arises, how does cell behaviour

change in the progeny of these normally heteroploid cells? To bridge the gap between this and the classical view of constancy in the chromosomal determination of cell behaviour, Timonen[26] suggested that "the variation of chromosome numbers connects the cells more closely with the whole". It must be then supposed that a human cell is not a unit as such but gains its biological significance only as a part of the whole organism. On the other hand, the range of heteroploid variability and mitotic abnormalities is not to be considered pathognomonic of malignancy.

It was pointed out by Strong[25] that decreased host specificity (i.e. progression in transplantability) arises by somatic mutation of cancer cells in the way of disturbances in chromosome number rather than from intrachromosomal changes. Accordingly, simple variations in the number of chromosomes might profoundly change the cell behaviour. On the other hand, the unlimited perpetuation of malignant characteristics peculiar to each particular tumour indicates the invariability or relative stability of the chromosomal apparatus in the ultimate phase of neoplasia. Accordingly, the cells with the most balanced chromosome sets have biological advantages over other somatic cells in respect to ability for independent existence. It appears therefore that chromosomal variability is a fundamental factor of normality; excessive stability of chromosomal apparatus is a basic factor of abnormality in the sense of malignancy. The induction of malignancy might be characterized as a change in the particular morphogenetic field, i.e. the breakdown of genetic control of tissue integrity with subsequent permission of an evolution (differentiation) of some cells towards malignant cells. It is therefore not necessary to postulate mutation as an essential step in the induction of malignancy, which may originate by normal mechanisms of cytodifferentiation. Cytodifferentiation is by definition a developmental process by which the cells acquire their permanent distinctive characteristics. The mechanism of progression in malignant characteristics is unknown. However, analysis of its nature can be aided by comparing it with embryonic induction and differentiation. The thesis that cancer induction is a process and not a single event bears directly on the recognition of basic similarity between embryonic differentiation and tumour induction. Foulds[7] suggested that in both instances similar biological laws operate at all stages of development. In this sense the induction of a tumour is a process of successive determinations. When this process is completed, the neoplastic potentialities are determined, but are not necessarily morphologically apparent without an additional stimulus. A sequence of new determinations causes the tumour to progress towards its ultimate phase. The intimate mechanism of cytodifferentiation has been compared to rearrangement of intracellular antigenic surface configurations which normally maintain the integrity of cellular structure and which are responsible for its transmission to descendent cells. The embryologists call it "immuno-differentiation" which constitutes a basic factor in histogenesis. According to Hauschka[12] the viability, persistence and perpetuation of a chromosomal antigenic variant play an important role in malignant invasive growth. Interestingly, the concept of antigenic surface configurations was found to be applicable to explanation of gene reproduction, protoplasmic replication, surface interactions among cells, antigen-antibody binding, and enzyme-substrate relations.

THE CRITICAL PHASE

As previously discussed, formation of a focus of malignant cells signifies the termination of the induction phase of neoplasia. The condition at this point might be briefly characterized as follows. The tissue has undergone neoplastic change of an unknown nature, whether formation of an aberrant transmissible metabolic pathway, somatic mutation, viral or plasmagenic infection, or deviated cytodifferentiation. At this time the tissue possesses to a certain degree some neoplastic characteristics such as heterotopia or anaplasia, but still retains a considerable number of characteristics of normal tissues in the sense of functions, properties and dependencies similar to the cells of origin. The fundamental characteristic of malignancy at this stage, which prompted us to designate it a "critical phase", is that the further progression of neoplasia depends on the interplay of promoting and inhibitory factors. It has been observed in human neoplastic diseases, and particularly well documented in studies on uterine tumours, that some malignant cells fail to progress to a stage of clinical cancer. In experimental work the presence of such cells led Gardner[9] to the defini-

tion of "dormant cancer cells". It appears that a neoplastic focus may remain completely inactive for an indefinite period of time. An appropriate stimulus such as hormonal imbalance appears to start anew the process of progression. The persistence of this condition may bring the malignant tumour into the ultimate phase in which the necessity for continuation of this imbalance does not exist.

These considerations indicate the meaning of the critical phase in neoplasia: during this phase the tumour progresses quantitatively and qualitatively in malignant characteristics, while still dependent on the enhancing and inhibitory stimuli. New malignant potentialities, such as ability to metastasize, may develop in addition to the progression in existing characteristics such as growth rate or invasiveness. It was suggested by Foulds[7] that a tumour may possess or acquire a varying number of recognized characteristics of malignancy; therefore it is not sufficient to classify a tumour as malignant, without specifying which malignant characteristics are present and to what degree. As pointed out previously, progression in malignant potentialities and manifestations may depend on common or separate factors. The result of the progression is either the ultimate phase of malignancy, the extinction of the malignant focus, or any intermediate between these two possibilities.

The action of promoting and inhibitory factors during the critical phase is evident in many clinical and experimental tumours. It was observed that regression of metastatic lesions occurs in some cases of breast cancer after hypophysectomy. On the other hand, it was found that metastatic lesion transplants "take" in 100% of cases on heterologous transplantation into anterior eye chamber. These findings demonstrate the difficulty of designating tumours with metastatic lesions as independent of extrinsic stimuli, as some of them respond to withdrawal of the promoting stimulus. It is unlikely that hypophysectomy removes the malignant potentialities of tissues. More likely a factor promoting directly or indirectly manifestations of some malignant characteristics is withdrawn and an apparent regression of the tumour occurs. A reapplication of the stimulus would probably cause recurrence of clinical manifestations of the disease. It is also of the utmost clinical importance to recognize the fact emphasized by Foulds[7] that "a grossly regressing tumour may be accompanied by further progression in potentialities, evident by the appearance of some progressing nodules in addition to regressing ones".

The actual state of knowledge of factors promoting and inhibiting the progression in malignant characteristics is very limited. We lack means by which to judge the biological degree of malignancy in each particular case, i.e. how to recognize the state of dependence, latent neoplastic potentialities, and the factors which are most likely to affect the clinical course in each particular case.

THE ULTIMATE PHASE

The concept of an autonomous period in neoplastic diseases is closely related to the concept of anarchy of cancer cells. By definition, the neoplastic focus finally reaches a state in which progression in malignant characteristics is completely independent of the host, apart from the blood supply derived. Evidence is accumulating that several biological factors operate also in the ultimate phase, hence the tumour is not completely "autonomous".

The existence of spontaneous regression (i.e. spontaneous biological control) of human malignancy is to be considered an established fact. Many older reports lack sufficient details to permit close scientific scrutiny. Such is the case described by Mackay,[17] where metastatic cancer disappeared after absorption of an exudate. Another is the report of Hodenpyl,[13] who treated human neoplasms with ascitic fluid removed from a patient with regressing carcinoma. Rohdenburg[19] reviewed numerous cases of spontaneous regression and arrived at the conclusion that, on rare occasions, histologically diagnosed malignant tumours regress spontaneously. Recently, Stewart[24] reported his personal experience and results of long-term studies on the spontaneous regression of human neoplasms. He quotes the following interesting cases: a uterine myosarcoma which regressed completely; a neuroblastoma, where a primary tumour healed after x-ray irradiation of a metastasis; an inoperable malignant hepatoma shrinking into a fibrotic nodule with only traces of atrophied tumour cells; a metastatic recurrent sarcoma of bone, disappearing completely after Coley's toxin administration. His description is so vivid that we might be allowed to quote it:

The first case I saw was one of uterine myosarcoma treated by Dr. George Pack. The tumour was wholly inoperable, being spread throughout the pelvis and in the mesenteries. The lesion was soft, very vascular, and hæmorrhagic. After biopsy was performed, the patient was treated by a radium bomb. As might have been expected, nothing happened. There was no evidence of any radiosensitivity, and the mass failed to regress at all. Then just before the completion of treatment and within the course of almost hours, a dramatic change occurred. The patient developed a high fever, an urticarial rash, a high eosinophilia, and within a few days lost kilos of tumour and ascitic fluid. The tumour completely disappeared; and when last I heard at least 10 years later, the patient was well.

Berenblum[2] advanced the postulate that in rare but verified cases of spontaneous regression of malignant tumours an acceleration of the rate of cancer cell maturation occurs, so that the number of undifferentiated cells falls below the critical number required for progressive growth. Dunphy[5] concluded, in a recent review of clinical material, that the traditional notion that cancer is an autonomous growth, which spreads constantly and progressively throughout the life of the host, is untenable in view of cases of "regression of metastases after removal of primary growth, late metastases, great variabilities in the growth rate of various nodules of the same cancer, regression of skin metastases and of indisputable evidence of natural defence against cancer".

The very fact that a malignant tumour may regress spontaneously, apart from various possible operating mechanisms, provides the strongest point against the concept of autonomy of malignant cells. The observations quoted above illustrate one of the important facts in recent advances in cancer research. They offer wide possibilities for a scientific approach to the problem of biological cancer control and thus for etiological cancer treatment.

One of us has attempted to integrate the fragmentary knowledge on the regulating factors in the ultimate phase of malignancy into a common frame of reference called "anti-tumoural situations".[14] First the question was raised whether the cancer tissue itself exhibits some self-regulation and might eventually contribute to its destruction. The following examples of possible factors can be quoted: presence of tumour inhibitors in malignant tissue,[15] so-called "cancer kappa", Weiss's templates and antitemplates regulating growth, natural growth inhibitors and accelerators, and diffusible gene products. Secondly, it was considered whether the tumour was affected by changes in the local environment such as effects of inflammation, local immunization, spreading and anti-spreading factors, or substances released by injured tissues. Finally, effects of extrinsic factors on the ultimate phase of the neoplastic process were discussed. The role of the endocrine system, neurogenic and vascular factors, immunobiological conditions, and factors affecting the metabolism of the host represent the principal points in the consideration of this question.

To find methods of analysis and reproduction of conditions comparable to those occurring in spontaneous regression of neoplasms appears to be an important field for investigation. On the basis of observations on tumours induced by 2-acetylaminofluorene it has been suggested that development of malignancy depends on the presence of three separate conditions: (1) injury of the cells in question; (2) imbalance of hormones, regulating proliferation of the tissue concerned; (3) susceptibility of the tissue in question.[23] The concept suggested by Hauschka[12] provides a further point in consideration of these conditions. According to Hauschka, malignant invasive growth results from the coincidence of three events: (1) viability of a chromosomal antigenic variant; (2) the accident of mitotic stimulus; (3) the concentration of growth-regulating substances in the common humoral pool. Hence, any event intrinsic or extrinsic to the neoplastic focus, interfering with any of these conditions, participates in regulation of the neoplastic growth in the ultimate phase and eventually could be responsible for regression of the tumour.

SUMMARY AND CONCLUSIONS

A strict division between the carcinogens and co-carcinogens does not seem to be feasible, in view of the "conditional" action of carcinogenic agents, depending on the presence of other factors. Recently accumulated evidence indicates that cancer may arise in certain environmental conditions without application of any known carcinogenic substances. It appears probable that during the life span of an individual some cells almost inevitably undergo cancerization. One should attempt to answer the question why no malignant tumour develops in an overwhelming majority of tissues exposed to the action of inducing agents. It is suggested that a co-ordinate action of several factors, affecting separate bio-

logical processes, is necessary for induction of malignancy.

The developmental character of malignancy makes feasible the division of the neoplastic process into phases, for the purpose of classifying various inhibitory and promoting effects. The authors distinguish the following three phases of neoplasia: (1) an induction phase, which includes the period of carcinogenesis; (2) a critical phase, during which further progression of malignant characteristics depends on some extrinsic factors; (3) an ultimate phase, which signifies a period of malignant growth, independent of any known stimuli. It seems to be a biological necessity for each tumour to pass through a phase of dependency. Since no dependency relationship has been established for the majority of tumours, the existence of a phase of autonomy is acceptable, although the validity of this term might be questioned.

Progression of malignant characteristics is probably one of the most specific properties of malignant tissues. Each of the malignant characteristics enumerated, such as growth, heterotopia, anaplasia, unresponsiveness to extrinsic stimuli and faculty to elicit local and systemic reactions in the autologous host, finds analogues in normal physiological processes. The progression may be present in several or one of the malignant characteristics; it may be continuous, or periodic, or even cease permanently. Manifest malignant characteristics, such as invasiveness or metastasis, can be influenced independently of malignant potentialities. The latent malignant characteristics appear to exceed the manifestations of neoplasia. As stated by Rous,[20] "most cancers seen by the surgeon are not doing all of which they are potentially capable, as witnessed by the stimulating effect upon their latency of trauma, necrosis, ulceration, bacterial infection". Under normal conditions the control reactions of the organism appear to balance malignant potentialities of the cells. The extent to which the sequelæ of their existence are overcome by the defensive mechanisms seems to determine the natural history of the neoplastic process.

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RÉSUMÉ

Il semble impossible d'établir une division précise entre les carcinogènes et les co-carcinogènes, à cause de l'action conditionnée des agents carcinogéniques. Des preuves récemment colligées témoignent que le cancer peut surgir dans un certain milieu, sans intervention d'aucune substance carcinogénique connue. Il paraît probable que, pendant la vie d'un individu, certaines cellules subissent presque inévitablement la cancérisation. On devrait tenter de découvrir pourquoi il ne se développe pas plus souvent de tumeur maligne dans la plupart des tissus exposés à l'action des agents producteurs. On suppose qu'une action conjointe de plusieurs facteurs, touchant différents processus biologiques, est nécessaire pour produire une tumeur maligne.

La manière d'évoluer d'une tumeur maligne rend possible une division du processus néoplasique dans le but de reconnaître certains facteurs qui peuvent en retarder ou en accélérer le développement. Les auteurs établissent les trois phases suivantes de la néoplasie: (1) une phase de début, comprenant la période de carcinogénèse; (2) une phase critique, pendant laquelle la progression des caractères malins dépend de quelque facteur extrinsèque; (3) une phase finale de développement de la tumeur maligne par elle-même, sans aucun stimulant connu. Il semble que toute tumeur doive, par nécessité biologique, passer par un état de dépendance. Puisque, pour la majorité des tumeurs, on n'a pas pu établir la relation de dépendance, l'existence d'une phase d'autonomie est acceptable, bien que la propriété de ce terme reste discutable.

L'évolution des caractères malins demeure probablement une des propriétés les plus typiques des tumeurs malignes. Chacun des caractères malins énumérés ci-après retrouve son analogue dans les processus physiologiques normaux: croissance, hétérotopie, anaplasie, indifférence aux stimulants étrangers, et la propriété de déterminer des réactions locales ou générales dans l'organisme. La progression peut se produire dans un ou plusieurs des caractères malins; elle peut être continue, ou périodique, ou même s'arrêter définitivement. Les caractères malins évidents comme l'envahissement ou les métastases peuvent être affectés indépendamment des possibilités malignes. Les caractères malins latents semblent dépasser les manifestations du néoplasme. Rous affirme: "La plupart des cancers vus par le chirurgien ne font pas tout ce qu'ils sont en puissance de faire, ainsi qu'en témoigne l'effet stimulant, sur leurs possibilités cachées, des traumatismes, de la nécrose, de l'ulcération, de l'infection bactérienne". A l'état normal, les réactions de contrôle de l'organisme semblent contrebalancer les puissances malignes des cellules. La limite où ces puissances malignes peuvent être vaincues par les mécanismes de défense semble déterminer l'histoire naturelle du processus néoplastique. M.R.D.

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PUBLIC OPINION ON CANCER IN CANADA

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IN 1954 A SURVEY of public opinion on cancer was conducted in the Manchester area of England by the British Institute of Public Opinion on behalf of the social research department of the Christie Hospital.[1] At the request of Dr. Ralston Paterson, Director of the Holt Radium Institute of the Christie Hospital, the survey was repeated in Canada by the Canadian Cancer Society. This is the report of the Canadian inquiry.

The survey was conducted in Canada by the Canadian Institute of Public Opinion (owned and operated by Saunders Marketing Research) and included a total of 2,663 interviews. The sample design was such as to give a national sample of 2,000 cases distributed, on a random basis, proportionately among the provinces, and 10 provincial samples, designed to represent each one for regional comparisons. The participants were classified into four age-groups and three socio-economic groups.

Age-Groups

21 - 29 years	24% of sample
30 - 39 years	28% of sample
40 - 49 years	22% of sample
50 and over	26% of sample

Socio-Economic Groups

Wealthy and average plus	20% of sample
Average	30% of sample
Poor and poor plus	50% of sample

Only women participated since the inquiry was centred on cancer of the breast and of the cervix uteri. The main aspects of cancer on which public opinion was investigated were curability, the value of treatment and the symptoms.

Four types of questions were asked of the women. The first type was related to general attitudes towards serious disease, such as: What disease kills the greatest number in Canada? Does early treatment make any difference to the chance of cure? Which of a given list of symptoms do you think most alarming? The second type of question was related to specific knowledge of cancer of the breast and female genital tract. In this group, questions were asked regarding the significance of a lump in the breast, the significance of a show of blood or discharge after menopause, and the most frequent sites of cancer in women. Thirdly, questions were asked about general attitudes to cancer and its treatment, causes and fears, such as: What is the main cause of cancer? Should there be freer public discussion of cancer symptoms and its possible cure? Should doctors tell patients when they have been found to have cancer? The final set of questions was related to the participant's personal experience with cancer, and participants were asked such questions as whether they knew of anyone being cured of cancer or of anyone with cancer.

In the section covering general attitudes to serious disease, it was found that, in Canada, 45% of the participants thought cancer was the leading cause of death while 40% thought heart trouble killed the most people. According to the latest vital statistics, deaths from heart trouble are approximately two and one-half times as great as those attributed to cancer. Among the provinces, it is interesting to note that 34% of those interviewed in Newfoundland considered tuberculosis the chief cause of death. Of the major diseases, cancer, as compared with tuberculosis, heart disease, asthma and rheumatism, was considered the most alarming. The opinion expressed on the curability of cancer varied considerably in the survey. In Canada 30% of those interviewed thought that cancer was never cured. Among the provinces this proportion ranged from 11% in Prince Edward Island, 12% in Alberta, 14% in British Columbia, 16% in Saskatchewan, 20 - 22% in Nova Scotia, New Brunswick, Ontario and Manitoba, to 34% in Newfoundland and to 55% in Quebec. In Canada 52% thought cancer was sometimes cured. In the provinces this proportion ranged as high as approximately 70% but in Newfoundland it was 34% and in Quebec 28%. Opinions on the effectiveness of early treatment in cancer also showed significant variations. That early treatment increases the chance of cure was the opinion of more than 90% of those questioned in Saskatchewan, Alberta and British Columbia but was held by only 63% in Quebec. In Canada as a whole the proportion was 80%. That early treatment of cancer makes no difference was the opinion of 30% of the Quebec participants but only 2 - 5% in the three western provinces.

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At first glance there appears to be some inconsistency between the replies on the curability of cancer and the value of early treatment. In Canada, for example, 30% offered the opinion that cancer is never cured while only 15% thought that early treatment makes no difference to the chance of cure. However, it is doubtful whether opinions on these two points bear a direct relationship, and the variation noted may be one to be expected.

The analysis of the data on the most alarming cancer symptom shows no significant variation between the provinces. Of the five major symptoms presented to the participants, a lump in the breast and a show of blood after the menopause were consistently considered more alarming than loss of weight or frequent pain after eating. However, in most provinces a constant cough was considered to be the third most alarming symptom. In analyzing the reasons for the selection of the most alarming symptom, it was found that over 80% of those mentioning a lump in the breast or unnatural bleeding interpreted the symptom as meaning cancer or something seriously wrong.

The data which were gathered on knowledge of cancer of the breast indicate that in all provinces except New Brunswick and Quebec over 80% of the women considered a lump in the breast as indicative of cancer (definitely), possibly cancer or tumour. In New Brunswick 77% of the women were of this opinion while in Quebec the proportion was only 59%. In Quebec, also, 29% of the women did not know the significance of such a lump; this proportion was under 10% in all other provinces. With respect to cancer of the uterus, one-third of the women in Canada did not know the significance of unnatural bleeding 10 years after the menopause. This high proportion may be explained by the fact that only 48% of the women interviewed were over 40 years of age.

The knowledge which the women of Canada possess on the subject of whether men or women are more liable to cancer indicates a misconception with respect to cancer in males. Whereas 52% of the Canadian sample considered women more liable to cancer, only 8% considered men more susceptible and 31% considered susceptibility in both sexes as being equal. In actual fact, the present annual mortality from cancer in Canada shows approximately 10,000 male deaths and 9,000 female deaths; in addition, the incidence of curable cancers of lip and skin is greater in males.

The category of questions covering general attitudes to cancer and its treatment, causes and fears reveals many provincial variations. Over 80% of the women in each province except Quebec felt that progress was being made in the war against cancer. In Quebec the proportion was 74%. In addition, approximately 80 to 90% of women in each province favour freer public discussion of the symptoms and possible cure of cancer. Six per cent of Canadians do not favour such discussion, while in Manitoba and Alberta this proportion rises to 11% and 12% respectively. Opinions about the main cause of cancer show substantial variations between provinces. In Canada 11% of women think a knock, bump or fall is the main cause, but in the three prairie provinces this proportion increases to 64% in Manitoba, 58% in Saskatchewan and 56% in Alberta. The variation here is to be found in the proportion of women who believe that the main cause of cancer is not yet known. Whereas in all except the prairie provinces the proportion is approximately 40 - 50%, in Manitoba, Saskatchewan and Alberta the proportion is only 2 - 4%. However, in another analysis relating to whether or not the participants agreed with certain statements about the cause of cancer, the opinion that the cause was not yet known was held by more than 70% of women in *each* province. This inconsistency may be accounted for in the structure of the questions. To the question "What would you say is the main cause of cancer?" approximately 60% of the women in the three prairie provinces answered "knock, bump or fall". In another question the participant was asked for an opinion on each of five statements which had been made previously about the cause of cancer, but *none of the statements mention knocks, bumps or falls while one does mention that the cause of cancer is not yet known.*

Approximately one-quarter of the women in Canada think that drinking will cause cancer while approximately one-fifth think immorality will cause it. Also, about 85% of Canadian women would willingly visit a friend with cancer and 58% feel that a doctor should tell a patient when he is sure that cancer is present. This proportion ranges between 53 and 73% in the provinces, except in Quebec where it is only 39%. As regards surgery in the treatment

of cancer, 25% of Canadian women feel that it increases the chance of spread while 36% feel that surgery stops cancer from spreading.

Analysis of the data by age of participants showed little variation in opinions given by the four age groups, except in the significance of unnatural bleeding 10 years after the menopause. Here 51% of the two older age-groups, 40 - 49 years and 50 years and over, considered this to mean cancer, as compared with 33% of those 21-29 years and 45% of those 30 - 39 years old. This variation seems to indicate that the question as worded was directed toward older women.

The opinions expressed by the three socio-economic groups do not show significant variations; this suggests that knowledge and opinions about cancer among Canadian women are approximately the same regardless of socio-economic status.

This survey has revealed certain national and provincial opinions and attitudes about cancer based upon selected samples of female participants. In some instances the results may be interpreted as a measure of the efficacy of the lay education programme of the Canadian Cancer Society while in others "public opinion" indicates the need for further education. The survey is presently being studied by the Canadian Cancer Society with a view to some modification of its lay education programme.

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RESULTS OF ŒSTROGEN DEPRIVATION THERAPY IN METASTATIC MAMMARY CARCINOMA*

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THE CONCEPTS which determine a rational approach to the problem of treatment in mammary carcinoma have been thoroughly reviewed in a companion article,[1] wherein an attempt is made to place the various methods available for use in primary and metastatic disease in their proper perspective. It has been stressed that, once metastatic disease becomes apparent, the emphasis in therapy of any kind must shift from a consideration of its possible effect on the neoplasm to that of its value to the patient. The degree of palliation achieved then becomes the prime factor determining the scope of any subsequent treatment which must, in order to warrant consideration, answer the three requisites of successful palliative therapy; namely, relief of suffering, restoration of function, and worthwhile prolongation of life. Œstrogen deprivation therapy, whether by oophorectomy or adrenalectomy or a combination of both procedures, has been discussed elsewhere[1] in these lights, and the present publication will deal with the results achieved rather than with the philosophical principles involved.

Similarly, the rationale underlying this type of surgical management has been discussed by several authors recently,[2-17] as have the technical considerations,[4, 12-16] whether they affect the preoperative and postoperative replacement regimen or the strictly surgical features of the operative procedure. Repetition of these details will not be considered in this report, apart from the brief summary below outlining the evidence noted in these previous articles implicating the œstrogenic hormones as factors of importance in the development of mammary carcinoma.

SUMMARY OF EVIDENCE IMPLICATING ŒSTROGENIC HORMONES IN DEVELOPMENT OF MAMMARY CARCINOMA

A. Experimental Evidence

Injection of œstrogenic hormones will produce carcinoma in mice, even in males of non-susceptible strains.

Oophorectomy in susceptible strains causes striking decrease in incidence of spontaneous carcinoma.

Oophorectomized mice subsequently secrete considerable amounts of œstrogen, the source probably represented by compensatory hypertrophy of adrenal cortex. Occasionally adrenal cortical tumours develop with evidences of pronounced œstrogenic secretion. These animals may even develop mammary carcinoma.

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Adrenalectomy is reported to be as effective as oophorectomy in diminishing incidence of carcinoma in susceptible strains.

Adrenalectomy retards growth of transplanted carcinoma and sarcoma; cf. lymphoid lesions.

1. Many were unaffected.
2. Relapse after initial remission often occurred early.
3. Better surgical methods developed.

Radiation castration is reported to produce comparable results (1936).

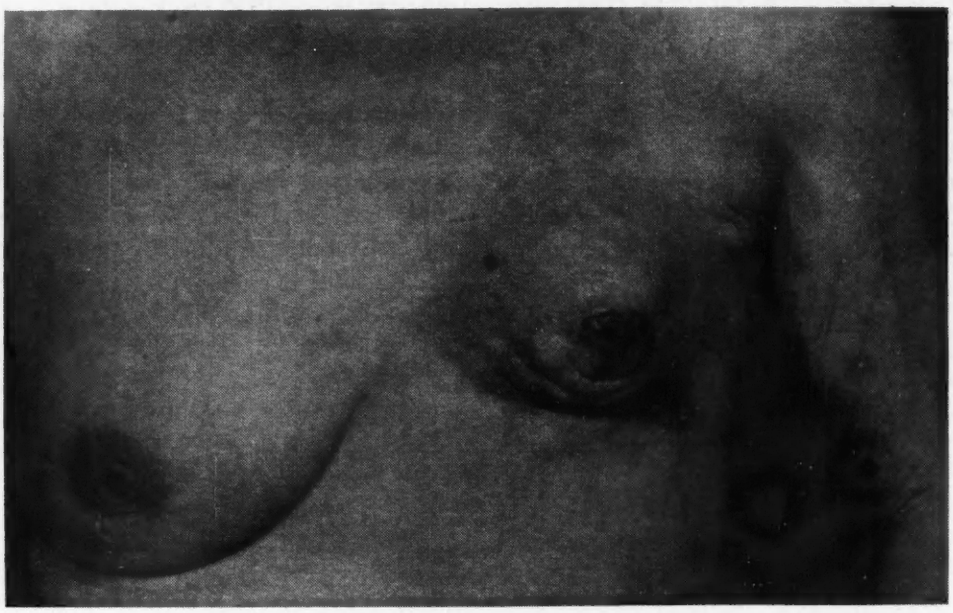

Fig. 1.—Breast Lesions and Axillary Nodes.—(a) Age 49, April 20, 1954. Clinical duration of disease—2 years. Primary carcinoma left breast with extensive retraction, skin invasion, peau d'orange and satellite nodules plus large mass of visible nodes in axilla behind anterior axillary fold. Induration entire right breast with peau d'orange particularly in dependent parts.

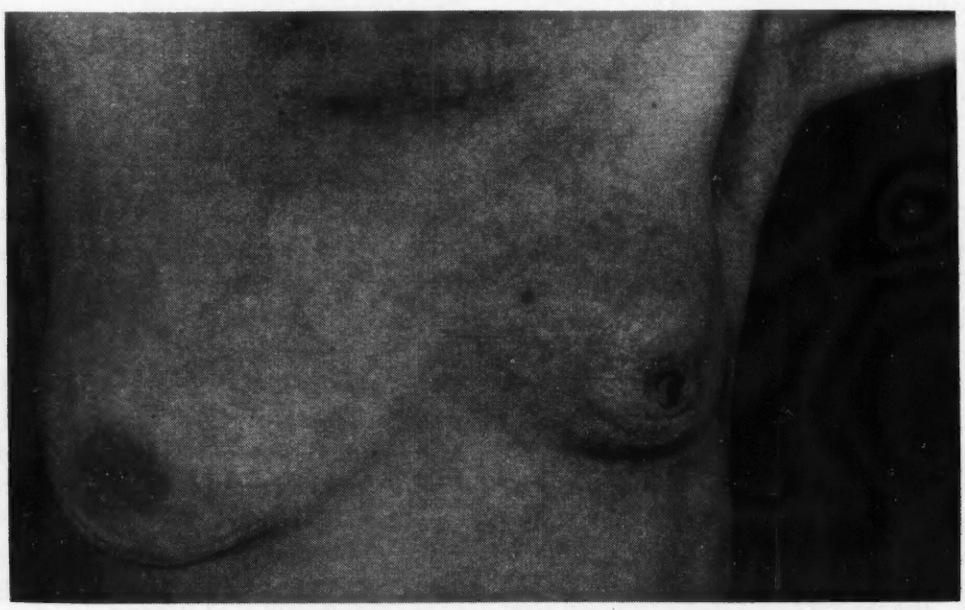

Fig. 1(b).—Photograph—September 14, 1954 (had oophorectomy and adrenalectomy May 7, 1954). Note diminution in hard mass involving left breast, disappearance of peau d'orange and satellite nodules and complete regression of large mass in axilla. Note also regression in induration of right breast with disappearance of peau d'orange and wrinkling of relaxed skin over dependent part of the breast.

B. Clinical Evidence

Administration of œstrogenic hormones may accelerate growth of neoplasm in primary and metastatic sites.

Surgical castration produced improvement in advanced cases (1896); and in approximately 1/3 of 96 patients up to 1905. The procedure was abandoned for three reasons:

Carcinoma is less frequent in castrated females, particularly if castration is done before puberty.

Following oophorectomy there is continued excretion of significant amounts of œstrogenic substances in urine.

Abnormal pattern of steroid excretion in urine in cancer patients suggests abnormal adrenal cortical function or altered metabolism of adrenal hormones.

Adrenalectomy in premenopausal women is ineffective

if favourable response is not obtained to previous oophorectomy.

With these experimental and clinical facts in mind it would seem reasonable to assume that beneficial results might be produced by depriving the tumour cells of the œstrogens normally a part of their environment. The following record concerns the results obtained in one such series of cases.

In young women, in the premenopausal period, there can be no doubt that the major source of œstrogenic hormones is gonadal, but nonetheless after castration the production of these substances continues, apparently from an adrenal cortical source. This is considered in the light of the concept of reciprocal endocrine relationships to indicate increased pituitary activity (and consequently functional stimulation of the adrenal cortex) in response to diminution in œstrogen control of pituitary function.[1] The length of time after castration that elapses before the adrenal cortex takes over this function to a degree sufficient for the subsequent stimulation of neoplastic cells, still dependent for their proliferative growth on the presence of œstrogen, is unknown and apparently varies considerably in different patients. The amount of steroid production from this adrenal cortical source varies also but is apparently never enough to stimulate menstrual changes in the uterus.

At any rate, one would expect that œstrogen-dependent cells would be affected unfavourably by oophorectomy in this age group, and one would also recognize the likelihood that signs and symptoms due to the neoplasm will reappear subsequently, either because of reactivation by œstrogenic stimulation from this new source or because a few cells in the tumour, already autonomous at the time of the original castration, had continued to grow and had finally reached a size sufficient for clinical recognition.[1] In this latter group, of course, further œstrogen deprivation would be completely ineffective, whereas in the former instances beneficial results might still be effected by removal of the adrenal cortex. That such an effect may indeed be produced in just this sequence has been very dramatically demonstrated by the Memorial Hospital group.[10-17] Approximately one-half of the premenopausal women they treated responded to castration with a demonstrable objective remission, and when recurrences developed in these patients approximately one-half would again show a favourable

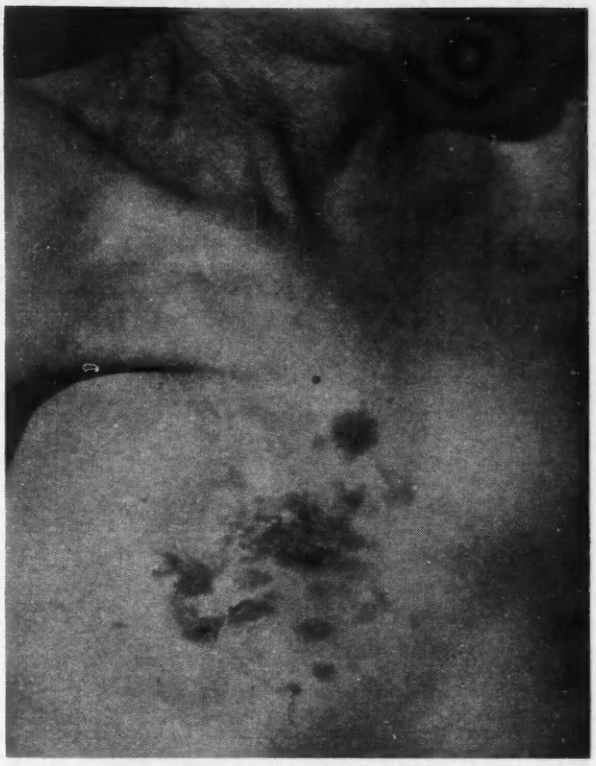

Fig. 2.—Local Recufrences.—(a) Age 47, March 2, 1953. Clinical duration of disease—6½ years. Multiple nodular recurrences in both skin flaps with occasional ulceration.

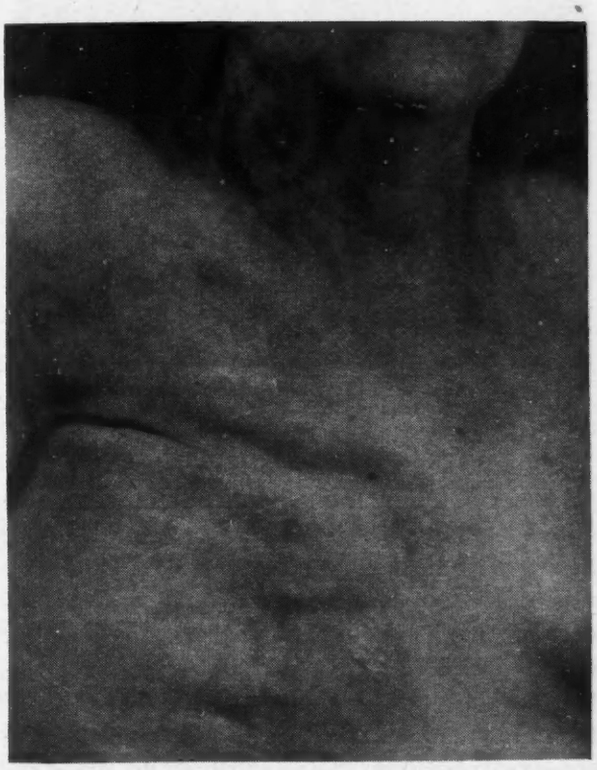

Fig. 2(b).—Photograph May 26, 1953 (had oophorectomy and adrenalectomy March 13, 1953). Note complete healing of ulcerating lesions and disappearance of all visible nodules.

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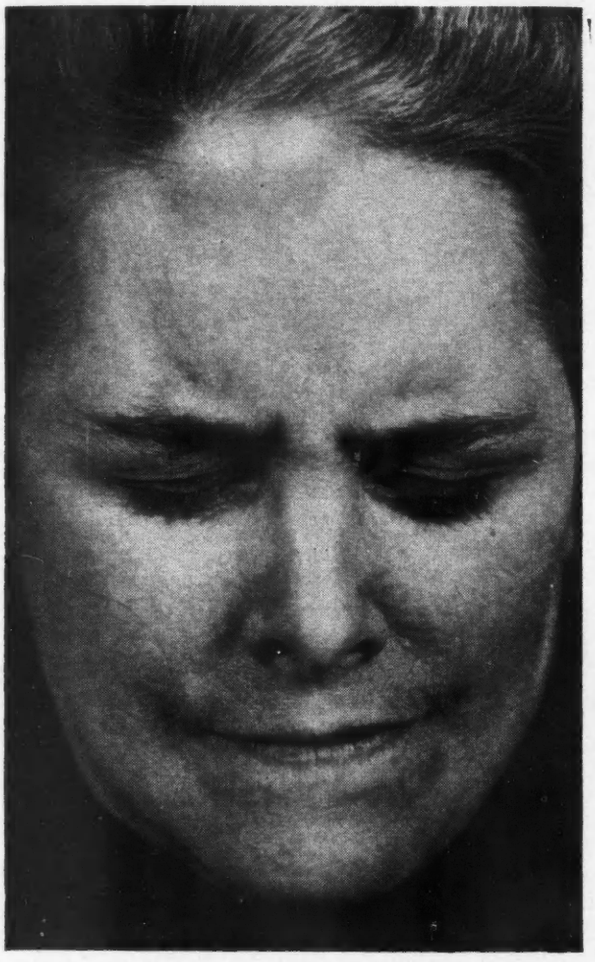
response to œstrogen deprivation following adrenalectomy. Adrenalectomy was, as might be theoretically predicted, found to be valueless if no evidence of œstrogen sensitivity was demonstrated by surgical castration.

Because we were uncertain of the possible duration of the original reprise in these younger patients, we chose to carry out total œstrogen deprivation therapy in the series now being reported, combining castration with simultaneous adrenalectomy, at first in a staged procedure but more recently at one stage. The castration was primarily surgical because of the unpredictable response of ovarian tissue to radiation therapy, although in a few cases in which extensive pelvic irradiation to bony metastases in the lumbar spine and pelvis had far exceeded the accepted castration dose we chose to place reliance on the effectiveness of the radiation, and oophorectomy was not performed. As it has now become apparent that the benefit derived from castration in cases of sensitive tumours extends over a period of several months and thus presents a valuable and relatively innocuous method of assessing the possibilities of adrenalectomy, we would now choose to stage the procedure in all premenopausal women and not consider adrenalectomy in those who failed to respond to oophorectomy. Although adrenalectomy is certainly not a difficult technical procedure or a major risk as regards operative fatality, it must always be considered a very major undertaking indeed because of the necessity for permanent replacement therapy, and the occasional development of serious difficulties in obtaining stabilization of the patient's needs for cortisone and salt, particularly whenever any intercurrent disease affects this delicate balance. Certainly adding to the patient's burden by undertaking a procedure of this potential magni-



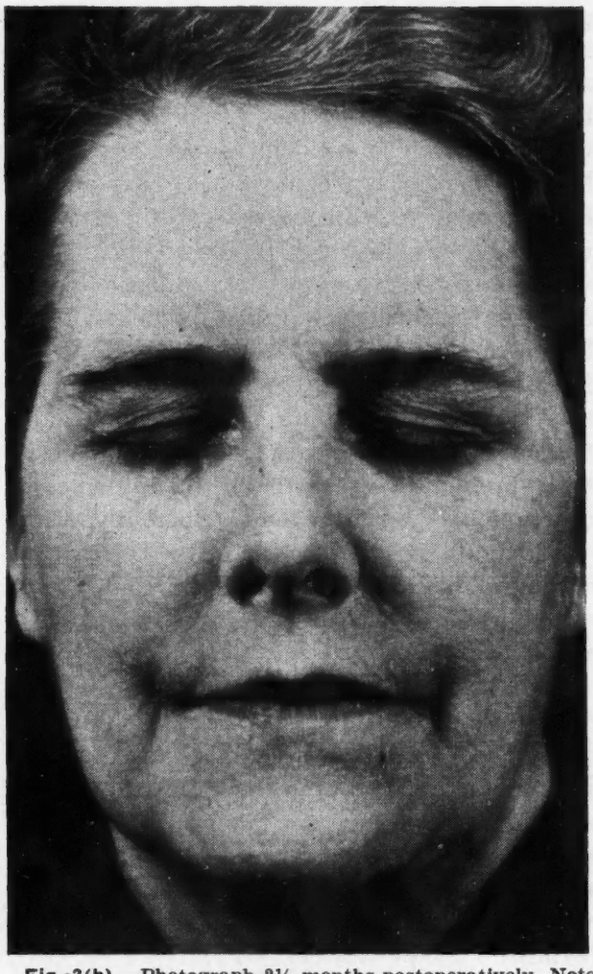


Fig. 3.—Skull Metastasis With Soft Tissue Tumour.—(a) Same patient as in Fig. 2. Preoperative photograph of frontal swelling over area of osteolytic skull metastasis.

Fig. 3(b).—Photograph 2½ months postoperatively. Note complete disappearance of swelling (radiological healing of osteolytic disease not as complete and swelling began to recur at 10 months).

tude without reasonable hope for commensurate benefit is therapy to be roundly condemned.

When one contemplates œstrogen deprivation in the postmenopausal patient, the problem becomes even greater and more serious, because no preliminary or simple trial of therapy such as castration is now feasible. At this age it is presumed that a major proportion of the œstrogenic substances still being produced reflect functional activity of the adrenal cortex; therefore, effective œstrogen deprivation can only be accomplished by adrenalectomy, possibly combined with oophorectomy. Some of this group of patients had previously had pelvic irradiation, and for the reasons outlined above reliance was placed on this form of ovarian control alone; in others no therapy whatsoever was directed at the ovaries when the patient had survived at least 10 years since the termination of her menopause. It is interesting to note that objective improvement was obtained in a proportion of these latter cases, indicating at least the fact that ovarian activity was insignificant at this age. The choice of suitable candidates for such a major attack upon the problem will be reviewed after description of the results obtained in this present series.

As in other reports, the patients chosen for study in this manner were all candidates who had undergone all accepted methods of treatment and who, at the time of operation, suffered from uncontrolled disease for which no other known method of management was available. Many were totally incapacitated by the pain of bony metastases and several almost moribund as the result of advanced cachexia or involvement of vital organs such as the lung, liver or central nervous system. The results obtained must always be viewed against this background, the procedure having been attempted only in these desperate situations.

In evaluating these results, emphasis was placed primarily on objective evidences of improvement because of the notorious difficulty encountered in the assessment of subjective changes, important though they may be to the patient herself. Having no baseline for comparison, it was also thought impossible to assess accurately the resultant prolongation of life in favourable cases although, since all patients treated were entering the end stage of their disease, those who survived longer than one year obviously had a significant increase in their life span, a purely statistical assessment of which however remains impossible.

For clarity in presentation the results are outlined below in Tables I-V. There were 32 patients in the entire series followed up for a period in excess of six months. Objective improvement was noted in 19, 60% therefore being favourably affected by the procedure.

TABLE I.

ADRENALECTOMY IN METASTATIC MAMMARY CARCINOMA

Number of cases	*Objective improvement*	*%*	*Average survival in months*	*Number improved alive to date*
32	19	60%	11 months	16

When patients were divided into a premenopausal and a postmenopausal grouping for the reasons previously discussed, objective improvement was apparent in 52% of the younger patients, and surprisingly enough in 73% of the older women. This latter figure was felt to indicate that the type of neoplasm likely to develop in older patients shared the impaired vitality of the host herself and consequently was more susceptible to any inimical change in its environment than would be expected in the biologically active neoplasms of younger hosts which, as a result of this activity, tended to develop autonomous characteristics at an earlier phase of their life history. A larger series, of course, would be necessary before any valid conclusions on this highly theoretical supposition would be possible.

In 10 of the 11 premenopausal patients and in 5 of the 8 postmenopausal women showing this objective improvement, the change could be described as dramatic, with prompt relief of the presenting symptoms (usually pain from osteolytic bony metastases which subsequently recalcified); regression and occasionally disappearance of soft tissue lesions whether primary or metastatic or local recurrences in the operative field; and consequently restoration of function, which was continued for a worthwhile period, presumably in association with a resultant prolongation of the patient's life. When assessing the length of time through which these dramatic effects should continue in order to allow one to consider the results "worthwhile", imponderable factors pertaining to the patient's

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TABLE II.

RESULTS OF ADRENALECTOMY: PREMENOPAUSAL OR MENOPAUSAL GROUP (AVERAGE AGE 42 YEARS)

		Evaluation				
					Objective improvement	
Type of procedure	*Number of cases*	*Too recent for evaluation*	*Death from disease within 30 days*	*No effect noted*	*Number*	*%*
Adrenalectomy with oophorectomy...	13	2	2	4	5	38%
Adrenalectomy—previous pelvic irradiation.....	10	1	2	2	5	50%
Adrenalectomy (subsequent radiation castration).....	1				1	100%
Cases available for evaluation.....	21		4	6	11	52%

TABLE III.

RESULTS OF ADRENALECTOMY: POSTMENOPAUSAL GROUP (AVERAGE AGE 57 YEARS)

		Evaluation				
					Objective improvement	
Type of procedure	*Number of cases*	*Too recent for evaluation*	*Death from disease within 30 days*	*No effect noted*	*Number*	*%*
Adrenalectomy with oophorectomy...	1	1				
Adrenalectomy—previous pelvic irradiation.....	6	0	1	0	5	83%
Adrenalectomy—no pelvic irradiation.....	5	0	0	2	3	60%
Cases available for evaluation.....	11		1	2	8	73%

TABLE IV.

ANALYSIS OF CASES SHOWING OBJECTIVE IMPROVEMENT. A. PATIENTS UNDER 50 YEARS OF AGE.

Type of procedure	*Number of cases*	*Number alive to date*	*Average survival*	*Comment*
Adrenalectomy and oophorectomy.....	5	5	13 mos.	One with reactivation at 12 months. One with ? reactivation at 18 months.
Adrenalectomy (previous pelvic irradiation).....	5	5	11 mos.	One with ? reactivation at 12 months.
Adrenalectomy (subsequent radiation castration)...	1	1	10 mos.	

TABLE V.

ANALYSIS OF CASES SHOWING OBJECTIVE IMPROVEMENT. B. PATIENTS OVER 50 YEARS OF AGE.

Type of procedure	*Number of cases*	*Number alive to date*	*Average survival*	*Comment*
Adrenalectomy (previous pelvic irradiation).....	5	4	11 mos.	One died at 17 months (reactivation at 5 mos.)
Adrenalectomy (no pelvic irradiation).....	3	1	9 mos.	One died at 6 months (reactivation at 5 mos.) One died at 9 months (reactivation at 8 mos.) One alive at 13 months (? non-malignant hip disease at 8 - 9 mos.)

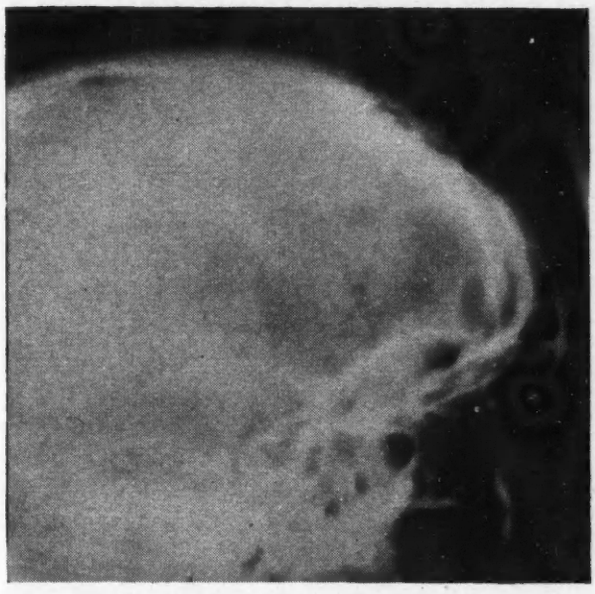

Fig. 4.—Osteolytic Skull Metastasis (No Soft Tissue Tumour).—(a) Age 35, February 4, 1954. Clinical duration of disease 2½ years. Large osteolytic metastasis left frontal bone.

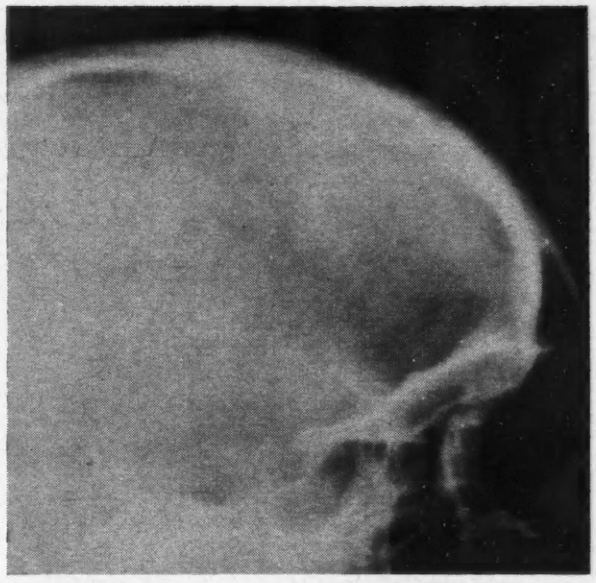

Fig. 4(b).—Radiograph, November 16, 1954 (had radiation castration in 1953 followed by adrenalectomy March 3, 1954). Note almost complete healing and recalcification of metastatic lesion continuing at 8 months postoperatively.

personality—and indeed the surgeon's philosophy—required appraisal. No fixed duration could be set as an empirical guide, although we chose to consider that complete relief of symptoms for a period of at least six months fell into such a category. In two of the older women, after an initial change that completely satisfied these criteria, reactivation developed after five months; one succumbed promptly to her disease and the other survived an additional year, carrying on a limited activity until shortly before her death, although completely invalided before operation. Consequently, one could consider 13 of the entire group as showing a dramatic improvement and 6 a remission satisfactory to the patient, although not as complete or of sufficient duration to satisfy the above criteria completely. These latter patients were those with incomplete

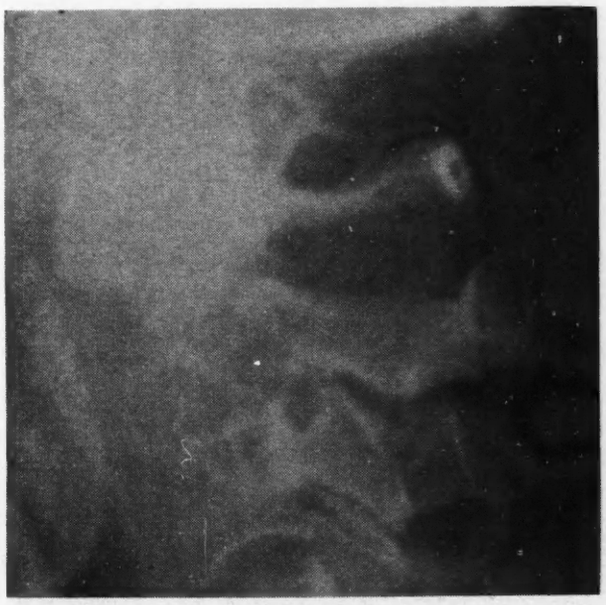

Fig. 5.—Osteolytic Metastasis Cervical Spine.—(a) Age 56, May 18, 1954. Clinical duration of disease—3 years. Extensive lesion involving particularly body of second cervical vertebra which has become almost completely radiolucent.

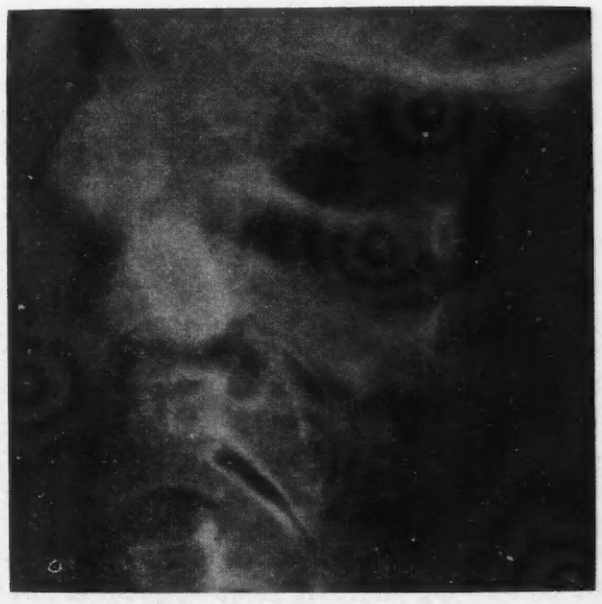

Fig. 5(b).—Radiograph, September 14, 1954 (had adrenalectomy June 16, 1954). Note dense recalcification of the involved vertebral body with reappearance of its anterior margin. Objective changes associated with immediate relief of disabling pain.

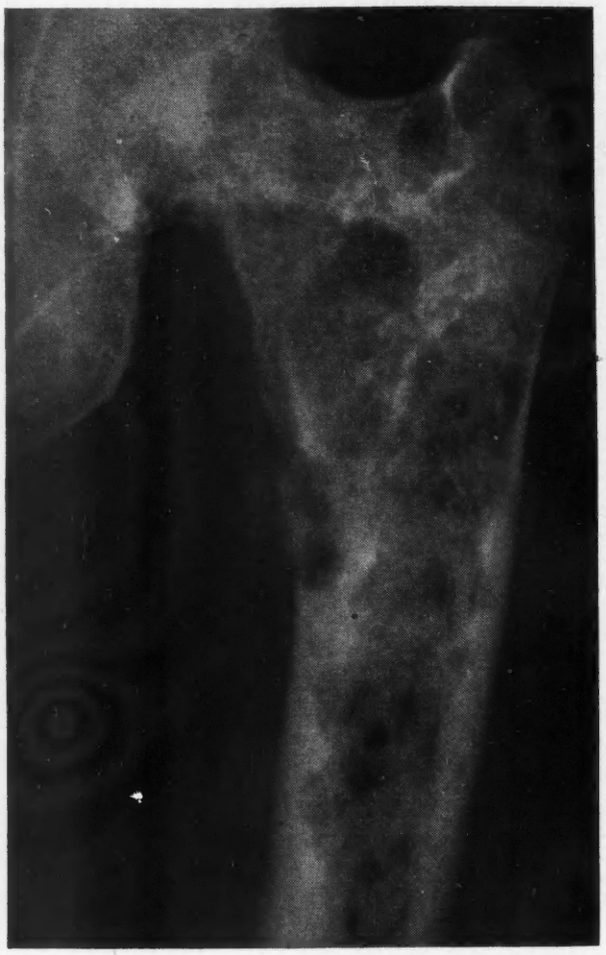

Fig. 6.—Osteolytic Metastases Upper Femoral Shaft.—(a) Age 50, January 15, 1954. Clinical duration of disease —3 1/3 years. Multiple osteolytic metastases throughout entire upper part of shaft of left femur extending into femoral neck.

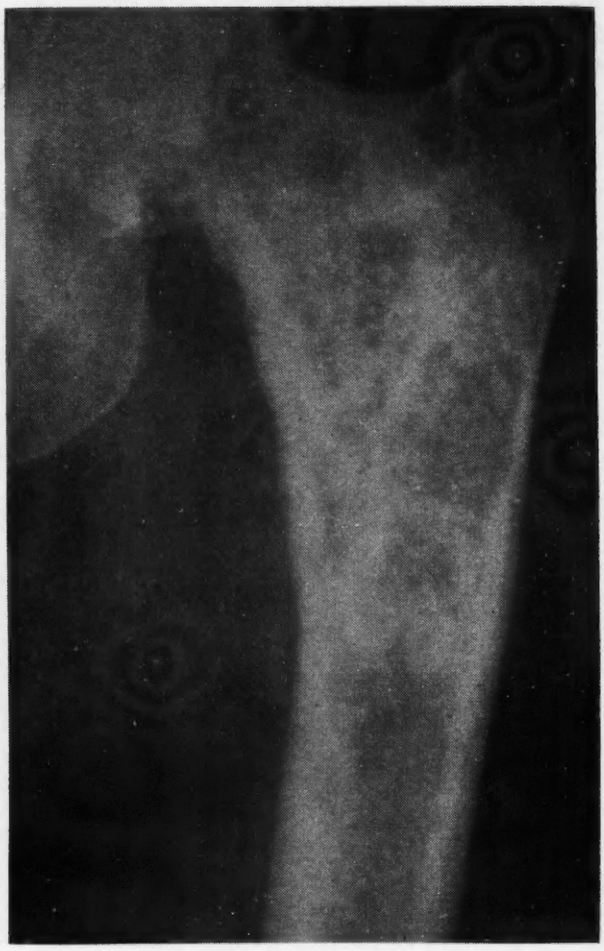

Fig. 6(b).—Radiograph, February 15, 1955 (had adrenalectomy January 28, 1954). Note again dense recalcification throughout entire area of involvement associated with complete relief of presenting symptoms.

relief of presenting symptoms, which were no longer disabling in degree; failure of complete healing or regression of soft tissue lesions; and in the two cases mentioned a rather early return of signs and symptoms to indicate continued activity of the neoplastic cells.

Completing the analysis then, one can divide the original 32 patients into 4 main groups as far as the effects of surgical treatment are concerned: (1) failure to survive the operation—5 (15.6%); (2) failure of the procedure to affect the disease—8 (25%); (3) objective improvement satisfactory to the patient subjectively, although objectively incomplete in scope or duration—6 (18.7%); (4) dramatic objective improvement—13 (40.6%).

The average survival time of 11 months in those showing objective improvement is misleading because, at the time of the surgery, 16 patients were still alive and as time passes the survival period must increase in this particular series. Two of the patients have lived two years since adrenalectomy without evidence of reactivation.

It is interesting to compare these figures with those reported by Sir Stanford Cade in a recent Hunterian lecture,[12] for the close parallel between the two series is broken only in the percentage of patients considered to demonstrate a dramatic improvement or a less complete remission. He reports objective improvement in 60.5% as compared to 59.3%, with remarkable improvement in 23.7% (cf. 40.6%) and satisfactory improvement in 31.6% (cf. 18.7%). The mortality rate of 16% (cf. 15.6%) and the "failure rate" of 28.9% (cf. 25%) are also almost identical.

A mortality rate of 15.6% demands explanation, but in all fairness it must be noted that death ensued only in patients already in the end-stage of their disease; not one patient died as a result of a technical problem encountered

at operation or of biochemical imbalance resulting from inadequacy of replacement therapy. One patient not included in the series became pulseless during the removal of the first adrenal, presumably because of a cerebrovascular accident, and the adrenal extirpation could not be completed. She made a slow postoperative recovery but lapsed into unconsciousness again on the fourth postoperative day and died 16 days after the attempted operation. Of the five cases included in the report one is considered a postoperative fatality only because the patient died while still in hospital six weeks after operation, after running a progressive downhill course with an increasing pleural effusion and extending pulmonary metastases, having suffered a wound separation after premature removal of the stitches. Of the remaining four cases, one unfortunate patient had dramatic and immediate relief from agonizing pain due to osteolytic metastases widely distributed throughout the skeleton, only to succumb suddenly on the 11th post-

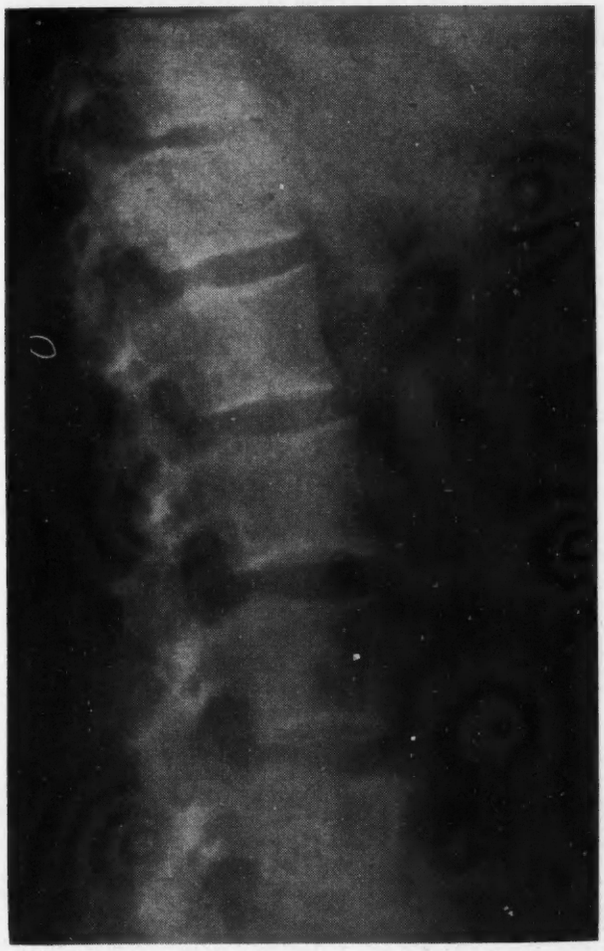

Fig. 7.—Vertebral Metastases Without Radiological Changes.—(a) Age 49, September 20, 1954. Clinical duration of disease—2½ years. Back pain without demonstrable metastases.

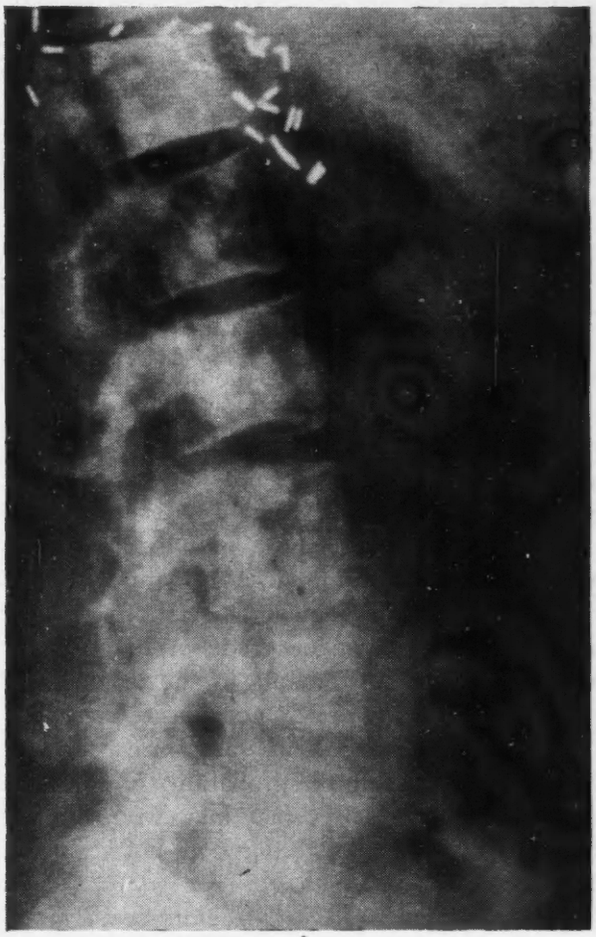

Fig. 7(b).—Radiograph, January 11, 1955 (had oophorectomy and adrenalectomy October 13, 1954). Note widespread calcification of metastatic deposits which were not visible previously (a similar change frequently occurs following radiation therapy of similar disease). There is a suggestion of decalcification in other areas of lumbar spine (cf. Fig. 8).

operative day to the mechanical insult of spontaneous and bilateral fracturing of multiple ribs anteriorly, allowing paradoxical sternal excursion and the respiratory inefficiency of a flail chest. A third patient developed convulsions requiring dilantin control and a right hemiplegia with aphasia between the stages of a combined procedure—changes thought due to hæmorrhage within a cerebral metastasis—and died 16 days after completion of the second stage. The remaining two patients with disseminated disease simply failed to respond to the operation and succumbed to their disease on the 10th and 13th postoperative days respectively.

Because of the realization, already mentioned, that this mode of treatment is purely palliative and must satisfy the tenets of adequate palliation, one hesitates to advise it when it may well add to the burden already imposed upon the patient by her disease. Therefore, it becomes imperative that one should attempt to discover

TABLE VI.

FACTORS INFLUENCING PROGNOSIS WITH ADRENALECTOMY. 1. CLINICAL DURATION OF NEOPLASTIC CHANGE.

Premenopausal and menopausal group		*Postmenopausal group*	
Objective improvement 11 cases	*No effect noted 6 cases*	*Objective improvement 8 cases*	*No effect noted 2 cases*
39 months —over 3 years —10 cases longer than 19 months	19 months —approximately 1½ years	72 months —6 years	not significant —1 case 23 months —1 case 144 months (liver death although diminution in size of liver.)

some method of predicting the outcome of such an attack, particularly in the postmenopausal group where a simple preliminary procedure such as castration can offer no guide to the prognosis. In reviewing factors of possible significance in this regard, those outlined in Tables VI-X have been considered. There appears to be no significant pathological correlation, at least as concerns the type or grade of the primary lesion (in contradistinction to the original reports of Huggins *et al.*[4-6]), nor does the previous response to androgenic therapy prove of significance in assessing the probability of a favourable result. This latter fact may well support the thesis[1-18] that testosterone does not act primarily as an anti-œstrogen.

On the other hand, two factors seem to be of real significance in determining the prognosis following œstrogen deprivation therapy. In the first place the clinical duration of the disease, dating from its initial clinical recognition, seems to favour a satisfactory objective response in direct proportion to the length of the history, presumably because the ability the patient has previously demonstrated to control the disease, if already harboured for several years, suggests that it is a relatively inactive neoplasm and therefore responsive to any inimical factor in its environment. The longer the history and the more effective previous therapy has proven in controlling metastases, and therefore prolonging the duration of the disease, the more favourable is the prognosis.

In the second place, the location of the metastatic lesions producing the presenting signs and symptoms appears to exert a definite influence on the outcome of this procedure; the most favourable responses are obtained when osseous metastases and local or accessible soft tissue lesions are present, objective improvement being noted in approximately two-thirds of such cases studied. Certainly the prompt relief of disabling pain and the healing of ulcerating skin lesions represent the most satisfactory effects observed in this series, and the duration of this improvement seems to be more prolonged than in other sites of involvement. It is interesting to note that these are the very types of metastases which respond most readily to other established methods of treatment; particularly is this true of radiation therapy.[1, 19] When intrathoracic structures (particularly the pulmonary parenchyma)

TABLE VII.

FACTORS INFLUENCING PROGNOSIS WITH ADRENALECTOMY. 2. SITE OF METASTATIC DISEASE

Site of metastases	*Number of cases*	*Objective improvement*	*No effect noted*	*Percentage improved*	*Assessment*
1. Bone	28	18	10	64%	Approximately ⅔ of cases show objective improvement. Duration of improvement longest when these non-vital organs involved.
2. Local recurrence or accessible soft tissue recurrence	17	12	5	70%	
3. Lung and pleura	13	7	6	54%	Approximately ½ of cases show objective improvement. Duration of improvement short-lived when these vital organs involved.
4. Mediastinum	2	1	1	50%	
5. Liver	4	2	2	50%	
6. Brain and central nervous system	4	0	4 Operation not completed in one case	0	No real benefit noted in any case.

TABLE VIII.

FACTORS INFLUENCING PROGNOSIS WITH ADRENALECTOMY. 3. PREVIOUS RESPONSE TO TESTOSTERONE THERAPY

PREMENOPAUSAL AND MENOPAUSAL GROUP				POSTMENOPAUSAL GROUP			
EFFECT OF ADRENALECTOMY							
Objective improvement 8 cases (3 had no testosterone)		*No effect noted 6 cases*		*Objective improvement 8 cases*		*No effect noted 1 case (had no testosterone)*	
EFFECT OF TESTOSTERONE THERAPY							
Remission	*No effect*	*Remission*	*No effect*	*Remission*	*No effect*	*Remission*	*No effect*
4	4	2	4	4	4	0	1
2 dramatic improvement 1 moderate improvement 1 showed remission with simultaneous radiotherapy		Both patients had simultaneous radiotherapy (in one remission was questionable)		1 dramatic improvement 1 moderate improvement 1 with remission in bony metastases but no effect on pulmonary lesions 1 showed remission with simultaneous radiotherapy (a repeat course had no effect)			

or the liver are involved, the improvement occurs in only about one-half the patients treated and seems to be much less prolonged. One would assume that this result stemmed from the fact that a vital organ is involved in these instances, and even though the neoplastic cells are favourably affected the extent of the damage may be so great that vital functions are permanently impaired; this impairment may quite possibly be aggravated also by the fibrosis that follows destruction of the tumour. Consequently, the host is surviving at a critical level which falls rapidly with any additional insult (potentially including the very fibrosis that must follow a satisfactory effect on the tumour) and the duration of improvement is likely to be much shorter. Certainly once the central nervous system is seriously affected this observation gains additional emphasis; not a single patient in this series had any real benefit from the operation once such involvement became clinically apparent.

With these observations in mind suitable cases for consideration fall into a combination of one or more of the following groups:

TABLE IX.

FACTORS INFLUENCING PROGNOSIS WITH ADRENALECTOMY. 4A. PATHOLOGICAL CORRELATION (PATIENTS UNDER 50 YEARS)

OBJECTIVE IMPROVEMENT 11 CASES				NO EFFECT NOTED 6 CASES			
Type	*Number*	*Grade*	*Number*	*Type*	*Number*	*Grade*	*Number*
Scirrhous	6	4	4	Scirrhous.	5	4	5
Medullary	1	3	0	Medullary	1	3	1
		2	3				
(no mastectomy in 3) (no sections available in 1)							

TABLE X.

FACTORS INFLUENCING PROGNOSIS WITH ADRENALECTOMY. 4B. PATHOLOGICAL CORRELATION (PATIENTS OVER 50 YEARS)

OBJECTIVE IMPROVEMENT 8 CASES				NO EFFECT NOTED 2 CASES			
Type	*Number*	*Grade*	*Number*	*Type*	*Number*	*Grade*	*Number*
Scirrhous	5	4	2	Carcinoma simplex	1	3	1
Adenocarcinoma	1	3	3				
Carcinoma simplex	1	2	2				
(No mastectomy in 1)				(No mastectomy in 1)			

1. Patients in whom all other established methods of treatment have been tried and have failed to control the presenting disease. This factor must never be overlooked.

2. Premenopausal women with previous favourable response to surgical castration.

3. Patients, particularly in the postmenopausal group, who have harboured their disease for many years since its initial recognition and in whom the previous use of established methods of therapy has produced remissions appreciable in effect and duration.

4. Patients in either age group in whom the metastatic disease affects the skeletal system or local and accessible soft tissues, including recurrent disease and nodal deposits.

Whether or not the procedure is to be contemplated in pulmonary, pleural, mediastinal or hepatic disease will depend upon the amount of treatment demanded by the patient and the urgency of the problem of symptomatic relief. In this situation, as actually in all other instances in which œstrogen deprivation therapy is considered, the factor of the patient's personal reaction to her disease cannot be overlooked.

5. Therefore, a fifth grouping of these patients becomes essential in determining those on whom to advise the procedure, and quite possibly this last consideration is actually the most important. Certainly any procedure which offers even in the most favourable combination of the above features no better than approximately a 50% chance of worthwhile palliation represents a gamble, the responsibility for which no surgeon can reasonably be expected to accept without the intelligent and wholehearted support of the patient herself. Consequently, it is to be contemplated only when the patient, fully aware of the nature of her disease, the likelihood that no other treatment will be of avail, and also the gamble inherent in this form of treatment, desperately wishing to do anything within her power to prolong her useful existence as long as possible, requests that the treatment be attempted. One can justly sympathize with such a feeling in young women who are parents of young children in whom the maternal influence is of such great significance to their future development; any honest attempt to prolong the effectiveness of that influence assumes major importance not only for the patient but also for her family. Many other personal factors may affect the decision and cannot be overlooked provided the fundamental problem is thoroughly

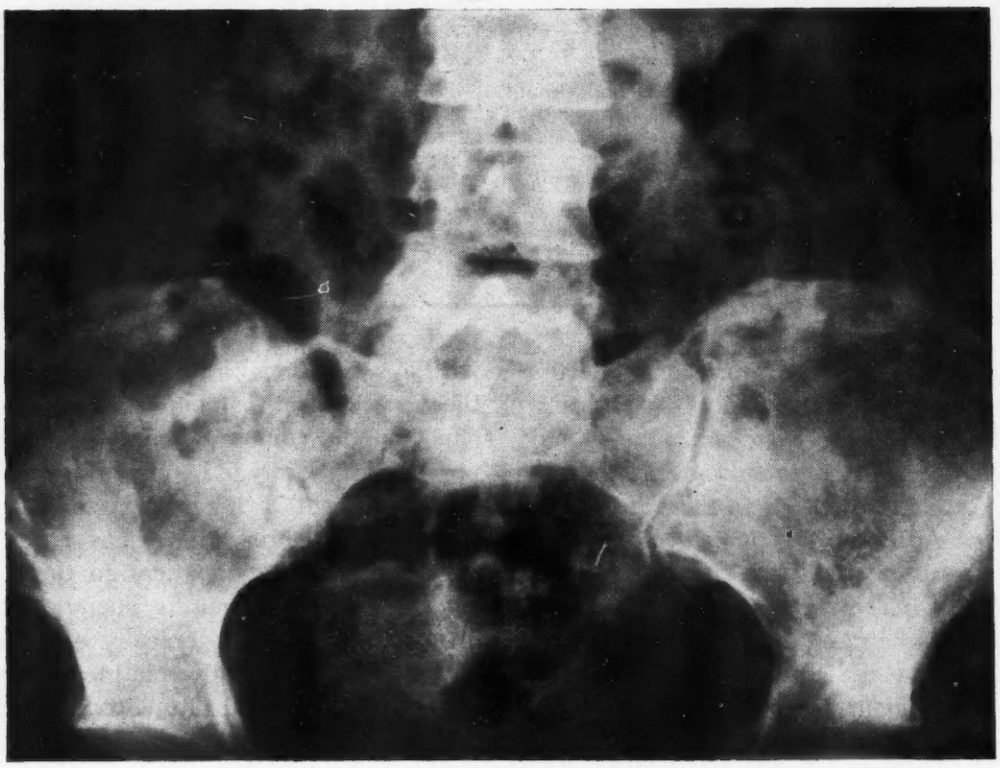

Fig. 8.—Osteolytic Metastases in Pelvis.—(a) Same patient as in Fig. 7. Preoperative radiograph with symptomatic pain from lesion in vicinity of right sacroiliac joint.

understood by all concerned in the treatment programme to be advised.

Under these circumstances, the criteria for determining the suitability of candidates having been rigorously followed, total œstrogen deprivation therapy may be reasonably considered. The gratitude with which these temporary reprieves are accepted by patients finding themselves in desperate situations of this kind can only be appreciated by those personally affected by the

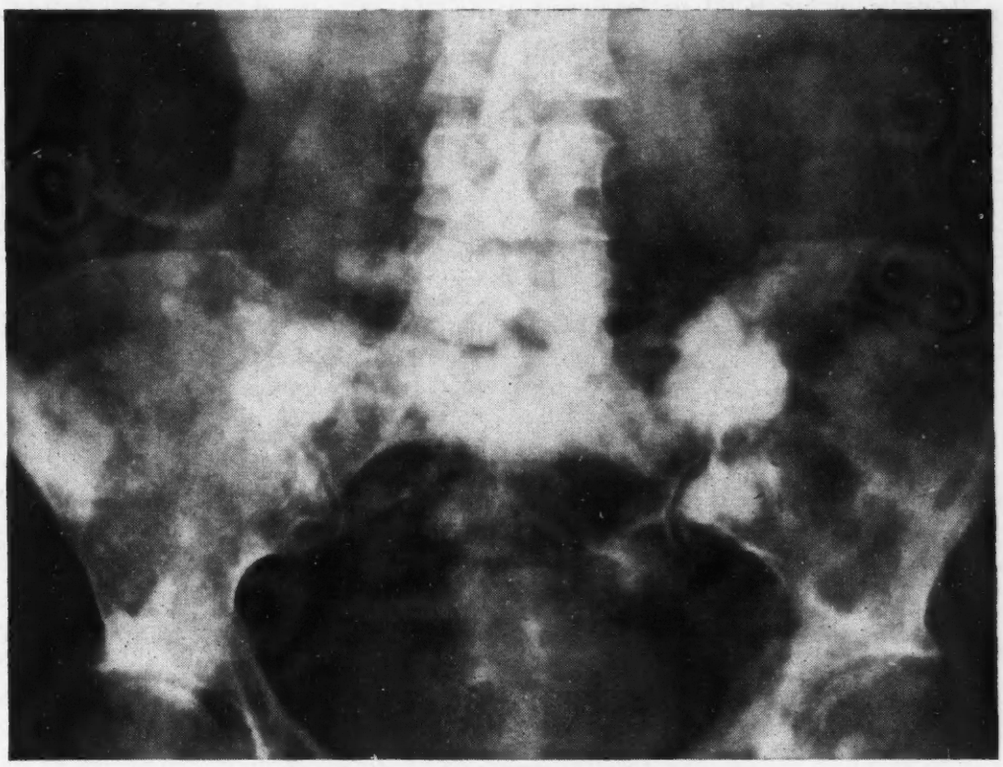

Fig. 8(b).—Note dense calcification in many areas of osteolytic metastases associated with dramatic relief of presenting complaints. It is particularly interesting to note extension of osteolytic process, however, in wing of left ilium despite healing of other lesions. This particular lesion was apparently autonomous and unaffected by the œstrogen deprivation therapy.

end stage of such illnesses. No-one but the patient can appreciate the tenacious grasp with which a fragile life-line can be held in these instances, and the glowing description of the personal happiness achieved during this period of remission has overtones of philosophical and religious significance that undoubtedly do much to assuage the stress of the imponderable situation with which they will be subsequently faced. If this stress is eased for the patient and her family, the value of the treatment, entirely apart from the objective evidences of improvement, cannot be overemphasized.

Whether or not other methods of treatment[1] will in the immediate future prove more effective (as they will undoubtedly do eventually) in these highly selected cases, œstrogen deprivation therapy may still be viewed at the moment as a useful and occasionally dramatically successful tool with which to fashion further clinical investigation and therapy, leading assuredly to eventual success in the control of this one malignant disease. It certainly provides an encouraging sign of progress in the unveiling of the mysteries still enshrouding our understanding of malignant disease generally.

SUMMARY

1. A brief summary is presented of the evidence suggesting that œstrogenic substances are of importance in the development of mammary carcinoma.

2. With these experimental and clinical facts as a basis, theoretical considerations favouring œstrogen deprivation therapy in both premenopausal and postmenopausal patients are reviewed.

3. The results of total œstrogen deprivation in a series of 32 consecutive patients are outlined in tabular fashion.

4. A similar tabulation is presented to indicate factors possibly of significance in determining

whether a favourable prognosis may be entertained.

5. The indications for consideration of this surgical attack upon metastatic mammary disease fall into five groups: failure of established methods of therapy to control the disease; previous objective improvement in premenopausal women following surgical castration; a long clinical history of the disease indicating the presence of a relatively inactive neoplasm; the presence of metastases in favourable locations, particularly those involving bone or local soft tissues; a patient, considered suitable as far as her personality is concerned, who is anxious to risk the gamble native to the procedure.

6. The therapy is purely palliative. It must therefore answer the requisites of successful palliation, in order that one may continue to contemplate its use even in these selected cases.

7. Photographic illustrations are included to demonstrate some of the dramatic effects obtained in this series.

The author would be remiss indeed were he not to express very deep appreciation for the financial support received from the Ontario Cancer Treatment and Research Foundation during this study. Without this assistance the project would not have been possible. One of the most valuable effects of this help referred to the relief afforded the patient in the expense of the cortisone therapy necessary as maintenance dosage in the postoperative period. We felt it was essential that financial considerations should not play any part in the patient's decision to undertake adrenalectomy, a decision surely difficult enough without such extraneous worries. Our gratitude for this assistance cannot be too strongly expressed.

My personal thanks are due also to Dr. W. T. W. Clarke of the Department of Medicine, Toronto General Hospital, who undertook to supervise the preoperative preparation, operative management and postoperative maintenance of the early patients subjected to this procedure. The fact that so few complications referable to the replacement programme developed in this series reflects the skill and conscientious application with which this supervision was performed. A purely medical appraisal of the problems encountered in these adrenalectomized patients will be forthcoming.

Dr. C. L. Ash, too, has assumed administrative responsibility for the study and has in addition, by his association with the Ontario Institute of Radiotherapy, made possible the referral of the major group of the patients treated. Without this source of material the study would have been impossible.

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SOME ASPECTS OF CANCER HORMONE RELATIONSHIPS*

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PERHAPS the most intriguing development in the cancer-hormone relationship is the increasing knowledge of forms of tumours which grow with all the characteristics of malignancy, except that their continued growth is dependent on a constant hormone stimulation. Some 15 years ago Dr. Collip and I encountered this phenomenon in the rat,[1] and I would like to review these old experiments as a typical example of tumour dependency. Initially, female rats were implanted with small pellets of approximately 5 to 10 mg. each of œstrone to ensure a continuous stimulation from exogenous female sex hormones. By actual measurement some 40 to 50 μg. of the hormone was absorbed each week. Before going further, I would like to stress that I intend to avoid any controversial discussions such as those which tend to arise when one compares animal and human lesions in terms of comparative dosage. In the first place, to convert rat dosage to its human equivalent requires the use of a special weights-and-measures table con-

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structed by Dr. A. S. Parkes.[2] This "avoirduparkes" system is as follows: 10 mice = 1 rat; 15 rats = 1 rabbit; 5 rabbits = 1 baboon; 4 baboons = 1 woman; 10 women = 1 cow, or 30,000 mice = 1 cow. These rat experiments, therefore, are similar to the absorption of 14 mg. weekly of œstrone in a woman, but I am not implying that such treatment would result in lesions comparable to those found in rats. In the rat, after some six to nine months, tumours, usually multiple, had appeared in the mammary glands of a high percentage of the treated animals and grew slowly but progressively, so that animals might live nine months after the first appearance of the tumours. The histological appearance was one of typical adenocarcinoma in most cases, epithelial proliferation, squamous metaplasia, or fibroma formation being noted. Tumours of different cell types might be present in different breasts of the same animal simultaneously. Metastases did occasionally occur to the lung. Tumour transplantation into rats of the same strain treated with œstrone failed, but autotransplantation into the subcutaneous tissue of the back was successful. Such implants were highly invasive. It appeared, therefore, that we had induced histologically characteristic malignant breast carcinoma which could be transplanted and would metastasize. Tumour growth was progressive until it caused the animal's death. These animals, however, still had palpable pellets of œstrone, and the next step was to remove this source of hormone surgically. The effects of this were dramatic. Tumour regression rapidly followed the removal of the hormone in four animals. In another experiment antagonism of the hormone by progesterone also caused tumour regression. Re-implantation of the pellet was followed by a resumption of growth by apparently the same tumours. Here was a typical picture of an apparently malignant transformation of mammary tissue, but the continued growth of the neoplasm was dependent on a continuous hormone stimulation.

For the purposes of this discussion I am using the term "malignant" in the pathologist's sense, as indicating a tumour with invasive and metastasizing properties and with the histological changes customarily ascribed to malignancy. In reference to experimental tumours, however, the term "malignant" has little meaning in the usual sense. As we shall see, tumours such as simple fibroma of the most benign histological appearance still show abnormal growth and will result in death of the animal. Again, as has just been described, invasive tumours, transplantable and metastasizing, remain malignant in the academic sense only as long as they are stimulated by a hormone. "Tumour" is probably the best experimental term signifying any group of cells which are growing more rapidly than their normal counterpart. These will eventually result in death of the animal, and may in succeeding generations show all histological transitions from benign to highly malignant structures. Irrespective of microscopic appearance and irrespective of the stimulus, these cells have an abnormal capacity for progressive growth when compared with other cells in the same animal.

There are many other typical endocrine tumours now described which show hormone dependence. Furth has recently reviewed this work in detail.[3] Dependent thyroid tumours may be induced in mice by a variety of procedures: giving antithyroid drugs or excess thyrotrophic hormone, and inducing iodine deficiency. Each manipulation has in common a resulting increase of pituitary thyrotrophic hormone and hypertrophy of the thyroid. Such tumours may metastasize (usually to lungs), appear histologically malignant and be transplanted initially only into hosts with induced excess of thyrotrophin. The induction and continued growth can be shown in a number of ways to be dependent on such increased TSH secretion.

Involvement of the pituitary-thyroid mechanism is also found in conditioned pituitary tumours in mice. Doses of I^{131} which cause atrophy and fibrosis of the thyroid, or even those interfering with its regenerative capacity, cause the multifocal development of adenomas in the pituitary. The formation of such tumours is related to thyroid hormone deficiency, since they may be prevented by thyroid hormone, desiccated thyroid, or thyroid grafting. Again, such adenomas can only be successfully grafted initially into athyroid hosts. Such dependent pituitary and thyroid tumours are readily produced only in mice; rats are apparently resistant to the same procedures.

Certain ovarian tumours may also be cited as dependent. Following ovarian transplantation to the spleen of castrate animals, the destruction of sex hormones by the portal system induces an increased secretion of pituitary gonadotro-

phin. The development of granulosa-cell tumours and luteomas subsequently takes place in the residual graft in mice, rats, guinea-pigs or rabbits. Such tumours may metastasize to the liver but do not transplant to normal animals. Hypophysectomy or œstrogen replacement apparently nullifies the hormonal pattern necessary for tumour development.[3-6]

Irradiation of mice may be followed by tumours, particularly of the ovaries or pituitary. Although a more complex situation exists, such tumours in general are conditioned by hormone imbalance and do not transplant into unconditioned hosts.[3, 7]

Prostate.—The prostate of man and experimental animals behaves very similarly in its response to sex hormones, hypertrophy following androgen therapy, or endogenous androgen production by the interstitial cells of the testes through stimulation by pituitary gonadotrophin. Cancer of the prostate was early recognized as a form of malignant growth which yet showed a marked sensitivity to hormones, even approaching that of the normal gland;[8, 9] the earlier work has been reviewed by Haddow.[10] In probably some 80% of cases, prostatic cancer is apparently dependent on endogenous androgen for its progressive growth.[11] Removal of androgen secretion by castration, although increasing pituitary gonadotrophin, may cause regression of both primary and secondary lesions. Depression of androgen production may also be induced by female sex hormone therapy through a depression of pituitary gonadotrophin, and probably through some direct form of antagonism. Cancer of the prostate in man, therefore, in most cases would appear comparable to other types of dependent tumours in animals. In the human there is no proof that the initial prostatic tumour results from an increased action of the male hormone; on the contrary, Moore[11] found that in 50 of 52 cases the carcinoma started in histologically atrophied glandular tissue. Both the primary and secondary malignant lesions, however, show increased growth under exogenous androgen stimulation.[8]

Breast.—Cancer of the breast in the human and its possible dependence on hormone secretion presents a more complex problem. The hormone control of mammary development in experimental animals still has many controversial aspects.[12] For example, œstrogens in the absence of gonads may cause maximum development of ducts and alveoli in the guinea-pig, but only duct development in the mouse. In the latter, and in most other species, progesterone and œstrogen are together necessary to induce full mammary growth. Large doses of œstrogens, however, may inhibit mammary development. Androgens, with the apparent exception of androsterone, produce mammary development similar to that produced by the female sex hormones, and in some species œstrogens may enhance androgen stimulation. The role of the pituitary is also complex and shows wide species variation. In the hypophysectomized rat, œstrogens have no effect on the mammary gland alveoli although ducts may be stimulated. On the other hand, a full response can be obtained in the hypophysectomized rabbit. Of the pituitary hormones which have been implicated in mammary gland function, prolactin probably has a direct action, allowing a normal response to œstrogen and progesterone to occur. Both ACTH and growth hormone, however, may be shown to affect mammary development although they most likely act indirectly on general metabolism rather than in a direct role. Similarly, thyroid function may be indirectly related.

Mammary gland development in the human is probably controlled basically by the same hormones, although the ovarian hormone level falls off after the menopause. Cancer of the breast, however, appears to be irregular in its dependency on hormones for continued growth. In many reported cases, pregnancy with its increase in all mammatrophic hormones has apparently speeded the advance of malignancy, but this might be attributed to an indirect effect such as increased blood supply. On occasions, however, attempted hormone therapy is followed by acceleration of, rather than a decrease in, cancer growth. Conversely, suppression of ovarian function by operation or radiation benefits a sufficient number of patients, particularly in the premenopause, to make the practice more or less routine in advanced cases. It is of historical interest that surgical removal of the gonads had been noted as beneficial in cancer of the breast or prostate as early as 1893 to 1895 (reviewed by Haddow[10]). Such cases are obviously examples of a form of cancer, the continued growth of which is dependent on œstrogens.

ABERRANT HORMONE PRODUCTION

Unfortunately, the hormone dependency of prostate and breast cancer is but a fleeting property at best. To the consternation of the clinician and the grief of the victim, the benefit of hormone withdrawal is but a postponement, all too brief, of the inevitable progression of the neoplasm to its final conclusion. In addition, some cancers of the prostate and breast do not initially benefit from hormone therapy or simple surgical removal of the implicated hormone-secreting sex organ. At this stage we are faced with tumours which either have reached an independent state or are being stimulated by hormones now being secreted aberrantly by a different endocrine organ. In the latter case the spark of hope of the sufferer may be rekindled by the benefit of a second operation removing the new source of hormone. The adrenal cortex is usually implicated, since it normally produces androgens and may secrete œstrogens. When cancer of the prostate, after an initial tumour regression following castration, shows a reappearance of malignancy, it may be suspected that the adrenals have gradually increased their output of androgen, the hormone on which the tumour is dependent. Such reasoning led Huggins and others[13, 14] to advocate in such patients bilateral removal of the adrenals. The results of this operation are now well-known, and again some 20-30% of tumours dependent on androgens show a regressive change. What is perhaps equally important, about 40 - 50% of cases show marked subjective improvement such as relief of pain.[13, 15-17] The urinary 17-ketosteroids, metabolic products of androgens of the testes and adrenal cortex, already at a reduced level due to castration, show a further drop after adrenalectomy. What is more important, androgen excretion is correspondingly reduced.[18] Recently, an ingenious modification of the adrenal operation has been described.[17] Here one adrenal was removed and the adrenal vein of the other shunted into the portal circulation. This resulted in the liver destroying both androgens and œstrogens with a fall in urinary 17-ketosteroids and œstrogen, but allowed a normal excretion of hydroxycortisone-like steroids; as a result, no exogenous adrenal hormone therapy was necessary.

In cancer of the breast a similar state of aberrant hormone production may exist. Œstrogens as well as androgens may be produced in the adrenal cortex.[19, 20] In experiments on strains of mice which develop spontaneous mammary cancer it was observed many years ago that ovariectomy reduced the incidence of cancer by removing the female sex hormone. However, when very immature mice were ovariectomized the incidence of cancer was high, apparently related to the assumption by the adrenal cortex of the function of œstrogen production. The alteration in adrenal function apparently took place much more readily in the young animal after ovariectomy (reviewed by Parkes[21]). It appeared logical, therefore, to expect that bilateral adrenalectomy of the previously ovariectomized patient with an œstrogen-dependent type of breast cancer might result in benefit to such a case. In many centres this operation has led to tumour regression in approximately 30% of cases, and is associated with a reduction in œstrogen secretion.[13, 15, 17, 20, 22, 23]

As has been pointed out, mammary development is a more complex phenomenon than development of the prostate and is dependent on pituitary factors. It seemed possible, therefore, that some breast cancers might be dependent on pituitary hormones and the patient would benefit if the pituitary gland were removed. This procedure is of recent introduction, but the few detailed studies reported suggest that hypophysectomy may induce remissions in perhaps 30% of cases.[24-26]

From an experimental point of view, one would not expect castrated and adrenalectomized patients with prostatic cancer to benefit from subsequent hypophysectomy, since pituitary secretion in such cases cannot affect androgen production. However, patients previously castrated have been reported as improved by surgical intervention.[24, 25] The clinical spectre of the gonadectomized, adrenalectomized, hypophysectomized cancer patient has therefore become a reality. The enthusiasm to attempt such surgical procedures in some of the small centres is somewhat disturbing, even to an experimentalist. The old teaching of surgical removal of the malignancy now seems in danger of being replaced by the dictum of surgical removal of everything but the malignancy, leaving it a truly independent tumour. In practice, of course, up to the present, major surgical intervention is a procedure considered as a last-resort block hurled by the tiring surgeon into the avalanche

of onrushing malignant cells. It is undoubtedly beyond my prerogative to be dogmatic about such surgical treatment of endocrine malignancy, but the operation has enjoyed a wave of enthusiasm in some quarters. However, as an experimental endocrinologist who has studied the new hormones which make replacement therapy possible and who has adrenalectomized and hypophysectomized many thousands of animals, I cannot help but be struck by the fact that such creatures at their best are only a mere shadow of the normal. The treated hypophysectomized animal is like a pleasure yacht from which the main engine has been removed and which is being driven by a small replacement auxiliary motor. It looks reasonably normal to the untrained eye and behaves well at a slow speed in calm waters. But what a disastrous picture is presented in the emergency of having to speed up to encounter stormy seas and withstand a severe buffeting with only a limited fuel supply. Undoubtedly, pan-endocrinectomy was an essential experimental investigation on dependent endocrine tumours, to be undertaken by experienced personnel at larger clinics, but before it is recommended as a routine therapeutic procedure the short-lived effects of successful treatment from the point of view of the patient should be carefully weighed against the possible consequences of the therapy.

Serious attempts are being made in many places to utilize methods other than surgery to reduce pituitary function. For example, various workers are exploring the effect of radiation therapy of the pituitary using cobalt-60 beam therapy. Unfortunately, pituitary function seems to be highly refractory to irradiation treatment. For some years we have been studying the actions of a substance extracted from a common weed—*Lithospermum*. It apparently possesses the curious property of specifically antagonizing the gonadotrophic action of the pituitary without itself causing any hormone effects. The antigonadotrophic action of this plant was originally utilized by Western Indian tribes as a successful method of preventing propagation. Although it is unlikely that this observation contributed appreciably to the decline of the North American Indian population, the action, theoretically at least, might eventually provide a method of reducing pituitary gonadotrophic activity and so be of value in cancer therapy.

Recently some reports which might prove stimulating but possibly misleading to the clinical advocates of hypophysectomy have intimated that pituitary secretion has a direct specific action on malignant growths in general. Experiments on hypophysectomized rats have been reported which suggested that the induction of cancer by an injected carcinogenic hydrocarbon was inhibited.[27] It seems unlikely that this represents any effect other than that described in older observations that hypophysectomy simply slows down the onset and growth of malignant tumours, but does not induce qualitative changes. In our hands and others, malignant sarcoma could be induced by 9:10 dimethylbenzanthracene and other carcinogens in hypophysectomized rats, although tumours appeared after a longer interval and in fewer animals when judged by controls.[28-30] Prolonged treatment with pituitary growth hormone has been reported from one laboratory to induce various forms of malignant tumours in rats,[31] and in one hypophysectomized patient pituitary growth hormone was found to accelerate the growth of osseous metastases.[25] There is only incomplete evidence, therefore, to suggest a direct participation of the pituitary in malignant processes generally, and hypophysectomy might at best be expected to diminish the tumour growth rate of non-endocrine organs only indirectly by general metabolic depression.

One may ask, however, in cancer of the breast of the gonadectomized patient—how does the benefit of hormone therapy fit into the concept of dependent tumours? In view of the sometimes paradoxical response of breast cancer to hormones it is difficult to determine the mode of action. The breast tissue of the pre-menopausal woman is preponderantly under the influence of female sex hormones. The action of testosterone in such cases of breast carcinoma may be chiefly to neutralize the action of any residual circulating œstrogens and to reduce pituitary gonadotrophins. In general the response to androgens in all breast cancers is about 15-25% objective regressions—particularly where osseous metastases occur. Such therapy is followed by a fall in urinary FSH and LH.[32, 33] Extensive androgen therapy may have undesirable side-effects which at least are recognized by the patient. As the husband remarked on meeting his androgen-treated wife returning from the hospital—he didn't know whether to kiss her or to shake hands. Œstrogen therapy

in breast cancer is of particular value in the postmenopausal case with soft tissue lesions, and perhaps 40-50% show regressive changes.[33-37] In such the most likely mode of action is through a depression of pituitary activity, as urinary gonadotrophins are reduced.

Adrenal steroid therapy with a possible action through depression of the adrenal cortex has been of less value in treatment of prostatic or breast cancer. Although an occasional patient may show objective changes, almost 50% show subjective improvement.[16, 23, 38, 39] Cortisone therapy increases urinary gonadotrophins.[38] Replacement therapy of the adrenalectomized patient may be accomplished with maintenance doses of cortisone without fear of markedly increasing androgen production. Although 17-ketosteroid values may increase, urinary androgens remain at a low level even after the daily administration of 100 mg. of cortisone.[18] The recent development of new fluoro derivatives and other steroids related to cortisone with quantitative and qualitative differences in action from cortisone may lead to a reinvestigation of the effects of adrenal and such steroids on malignancy.[40, 41]

Of some practical importance is the value of the response of hormone therapy as a means of predicting possible beneficial effects of adrenalectomy or hypophysectomy. The general opinion would seem to be that patients who respond initially to gonadectomy are more likely to respond to subsequent ablation operations or hormone therapy. On the other hand, some persons will respond to hormones and not to castration. In cases where deterioration occurs due to one hormone a response may be observed by administering the opposing hormone, and curiously enough, tumour regression on occasions may begin after cessation of therapy.[22, 23, 32, 33] Such beneficial effects of hormone therapy appear most reasonably explained on the assumption of an ultimate decrease in some hormone, steroid or pituitary, on which the continued growth of the neoplasm is dependent. Indeed in some cases it would appear that any induced hormonal imbalance may be beneficial even if there is no logical endocrine explanation. Perhaps the occasional response of cancer of the cervix to progesterone therapy is such an instance. As an alternative mode of action one would have to consider some antagonistic effect of the various hormones directly on the tumour. Evidence of this is not convincing, although some ingenious experiments have been designed on this assumption. The case of a water-soluble phosphate derivative of stilbœstrol might be cited. Here it was hoped that prostatic phosphatase would liberate and allow concentration of free stilbœstrol from its phosphate salt in the prostatic lesion, with a resulting powerful local action.[42]

DURATION OF RESPONSE

As is well known, the response of dependent tumours to ablation operations or hormone therapy is only a transitory one. In general the effects of the initial treatment such as gonadectomy tend to be the more prolonged; but great individual variation exists. Subsequent operation or hormone therapy may give relief for an average of perhaps seven to eight months and, rarely, up to two years. In many cases only a few weeks elapse before tumour regrowth begins,[43, 44] the terminal stage being a form of endocrine malignancy which does not respond to any known form of therapy.

INDEPENDENT ENDOCRINE TUMOURS

For the remainder of this paper I would like to discuss and speculate a little on the problem of the characteristics of the transition of the dependent to the independent type of cancer.

Some of the experimental endocrine dependent tumours referred to previously, and reviewed by Furth, may show a rather rapid transition to a growth which is independent of any demonstrable hormone control. The change is gradual, without any sudden change in gross or microscopic characteristics. As pituitary tumours induced by radiation become more independent, however, they show a sharply reduced ability to produce pituitary hormones. Some dependent tumours may not become autonomous during their span in the original host—as was found in the mammary rat tumours induced by œstrone pellets and previously described. On transplantation through successive generations, independence may become established. The ease with which successful transplantation can be accomplished becomes increased and there may be an apparent increase in malignancy on successive transplantations. Again, I would like to refer to some recent experiments in our laboratory, performed in collaboration with Dr. Jean Millar, which demonstrate a number of relevant and interes-

ting features in this connection.[45] It was originally noted that a spontaneously occurring mammary fibroma in a female rat could be transplanted and was successfully carried through 12 or more generations. This tumour was typically benign, with a long latent period, and showed a slow progressive growth which allowed it to reach a relatively enormous size without greatly interfering with the general health of the animal. The general microscopic picture of a typical fibroma with a minimum of ducts was maintained throughout all transplanted new generations. This tumour, although composed mainly of fibrous tissue, was in its early stages dependent on œstrogens for progressive growth. Thus it would not take and grow in ovariectomized female animals or in males of the same strain. Conversely, small doses of 1 μg. daily of stilbœstrol allowed growth and even caused a definite growth acceleration. This could also be induced by pituitary extracts and probably by pregnancy. After a number of transplantations, however, some adaptation had occurred, so that it now could be transplanted successfully to ovariectomized females or to males. Histologically it had not changed. Larger doses of œstrogen, 100 μg. daily of stilbœstrol, caused a complete inhibition of the benign tumour growth through the duration of the study. Here was an example of a benign tumour, even though a fibroma, which could be markedly influenced by hormones but which showed a slight though definite transition to hormone independence. At the same time, a much more striking change occurred in that many of the tumours exhibited a typical malignant transformation into a fibrosarcoma. Sections showed typical rapidly proliferating sarcoma cells. Transplantation was now followed by only a brief latent period, rapid growth, metastases and death of the animal in a markedly cachectic state. Such malignant tumours showed little or no effects comparable to the benign counterparts when the tumour-bearing animal was subject to the same hormone alterations. Here was a further change to an independent tumour, but this time associated with all the other characteristics of malignancy. The sequence of events in this tumour, therefore, was from a benign fibroma dependent on œstrogen to a fibroma not dependent on œstrogen but subject to hormone influence, and finally to a fibrosarcoma totally independent of hormone action.

What was the cause of malignant transformation in these benign fibromas? In these experiments one observation was striking. The malignant change occurred only in fibroma, the growth of which was retarded. This could be accomplished experimentally by using transplanted tumours in male rats or treating females with the large dose of œstrogens. After some months of inhibited growth, sarcomatous transformation took place and rapid progress of the malignancy occurred despite continued hormone alterations. Conversely, in no case of fibroma where growth was accelerated by pituitary or sex hormones or pregnancy was any malignant transformation found. This growth pattern, as demonstrated in the gross by the fibroma, of cessation of growth prior to malignancy of an independent type is not a new phenomenon. Many years ago various workers commented on essentially the same phenomenon observed in the breast tissue of mice of strains of high tumour incidence. In this case the atrophic changes were seen microscopically and it was suggested that in these areas malignant cells arose by some process such as mutation.[46] (The atrophied areas in the human prostate from which malignancy apparently arises have been commented on previously.) Haddow and colleagues have published extensively on the interesting properties of carcinogenic chemicals which all possess the additional property of inhibiting body growth and may even inhibit the growth of transplanted malignant tumours under certain conditions.[10, 47, 48] The work of Law and associates has shown that in experimental leukæmia chemotherapeutic agents may cause a check in the malignant process but this is shortly followed by a proliferation of different cells which are now independent of any therapeutic influence by that particular drug, and probably arise through mutations.[49, 50] In some cases these new cells may even exhibit dependency on the chemotherapeutic agent for continued growth. This sequence of events for malignant cells brings to mind the somewhat similar development of strains of bacteria refractory to antibiotics, and the gradual development of independence of plant tumours from the normal control of auxins or plant hormones.

In human cancer it would seem possible that the same sequence of events could occur. The action of hormones or antimetabolic chemotherapeutic agents in general closely follows a

pattern of initial effectiveness which gives way to a return of new growth now uninfluenced by the agent. On the other hand, different agents may act effectively in turn in the same way until a more virulent degree of malignancy is reached, unresponsive to all agents. Examples of leukæmia which may respond in turn to chemical agents, cortisone, and x-radiation, come to mind in this respect. In cancer of the breast or prostate is it not likely that a check in growth of the dependent stage by hormone manipulation serves as an initiating mechanism for the transition of new cells into malignant growths of an independent nature?

The final change in a cell which shows progressive abnormal growth, even though hormonally dependent, to one entirely autonomous, is probably the most fundamental problem in cancer research. Most workers favour the concept either that a mutation takes place or that some progressive metabolic alteration induces a permanent and irreversible change in the cell. A number of recent reviews in cancer research consider such theories very thoroughly.[1, 3, 51-54] Similar to the many suggested, but probably most apparent from the behaviour of the endocrine tumours just discussed, is the possibility that a malignant cell is one which has simply become habituated to an altered hormone or chemical environment, a form of individual cellular adaptation probably necessitated by some metabolic deficiency. It may be envisioned then that, of the normal cells composing prostate or mammary tissue, one or more, in the struggle for existence in an environment rendered inadequate by a hormone or other deficiency, surreptitiously become adapted to their environment and may perhaps acquire an altered utilization of components of their surrounding media for growth. Although showing increased growth they may still be dependent on some hormone influence. Deprivation of a necessary hormone is reflected by growth regression and even death of many cells. However, some cells already having an increased ability to adapt can now readily further adapt to a deficient environment and eventually can maintain increased growth despite any form of hormone imbalance. In its widest aspect any carcinogen or antimetabolite may act similarly by initially inhibiting cellular proliferation and so provide a suitable stimulus to initiate cells to adapt to an altered environment and resume growth. In other words, is a cancer cell simply one which initially had a greater ability to adapt to some deficiency in its environment and so ultimately to multiply unrestricted by the usual metabolic breaks which control regulated cellular growth? As conditions change, either physiologically or by therapeutic procedures, a few cells continue to perpetuate this increasing ability to habituate to new conditions until finally their metabolic processes for growth are so bizarre that they are in no way restricted. Cancer may be simply one form of the so-little-understood specialized types of adaptation which occur in the body, but in this case originating from an adaptation of an individual cell. Should such a hypothesis be valid, benignancy would seem assured by the maintenance of cellular environmental conditions which allow progressive cellular growth. Any condition checking cellular growth would be potentially a stimulus, leading to the initiation of cell adaptation. It might be thought that such a concept does not explain examples of tumours where the autonomous stage appears to follow immediately on an excessive growth of apparently normal cells. In such cases, however, it may be imagined that extreme stimulation of normal growth might lead to exhaustion of some essential nutritional ingredient for the cell and actually induce a relative deficiency, again leading to adaptation to other metabolic pathways. Unless it has the property of being initially lethal for all cancer cells, an anti-cancer drug may, therefore, at the same time as it destroys most of the cells, be serving as a stimulus to further adaptation of the remaining cells. To be fully effective such a drug would need to be combined with some method of inhibiting adaptation, if such a property is subject to exogenous influence. Perhaps it is this increased adaptive ability of the cancer cell which may ultimately lead to its extermination. If such adaptation processes could be controlled or channelled into some unusual chemical pathways, the cell might then be attacked by administered drugs or radioactive elements which it had been adapted to utilize specifically. Although this concept of the cancer process is a speculation, perhaps allowable in a paper such as this, intended to stimulate interest and discussion, it is surprising how much of our knowledge of cancer does fit into such a simple scheme.

At this moment I feel that a quotation from Greenstein would probably be in order: "The

bibliographer in cancer research is confronted with a monstrous and amorphous literature, controversial, often hastily ambitious, and frequently haunted by the ghosts of countless once-hopeful and dazzling hypotheses."

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Case Reports

CONGENITAL TUBERCULOSIS

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CONGENITAL TUBERCULOSIS may be described as an infection of the child with *Mycobacterium tuberculosis* contracted from the mother during intra-uterine life. Although at one time it was believed by some authors to be not an uncommon occurrence, today it is generally recognized as a rare mode of tuberculous infection. In fact, only 124 proved cases had been published in the world literature up to 1950.[1] Since then several more have become known. This relatively small number is due to the fact that only a few of the infants who show an early conversion of the tuberculin skin test or even have actual disease fit in with the criteria for the congenital origin of the infection.[2] These are: (1) the tuberculous nature of both the mother's and the child's disease must be proved; (2) signs and symptoms of the infant's illness should appear at a reasonable time interval—from birth to several weeks; (3) every external source of infection must be excluded if the disease occurred after birth. To these we would like to add a fourth condition, namely, the identity of the tubercle bacilli obtained from the mother's sputum and the gastric washings of the infant, with regard to sensitivity or resistance to antibiotic and chemotherapeutic drugs.

In the past, congenital tuberculosis was a disease with a poor prognosis. In fact, most of those affected by it were stillborn or died shortly after birth. Only those who were infected

during parturition survived for a short time. This poor prognosis will certainly be changed if the new methods of treatment and the anti-tuberculous drugs are applied early in the maternal disease.

It has been stated[3] that tubercle bacilli can penetrate the normal placenta. However, it is commonly assumed today that the usual source of infection of the fetus is a definite tuberculous lesion in this organ. Miliary disease in the mother is responsible for these placental foci in most cases. Another considerably less frequent occurrence is the infection originating from a tuberculous endometritis. Despite the fact that the placenta is involved in many cases, infection of the fetus occurs only rarely. This is remarkable if one considers the close communication between the maternal and fetal circulations. It has been shown, however, that the fetus possesses a high degree of resistance, and also that the oxygen tension in the fetal blood is low and therefore the condition for the growth of tubercle bacilli unfavourable.[4] Since the use of antibiotics in the treatment of tuberculosis, one is justified in expecting a further decrease in the number of cases of congenital tuberculosis because of the proved ability of some of these drugs, especially streptomycin, to penetrate the placenta.[5]

The fetus is most commonly affected by hæmatogenous transmission of the bacilli by way of the umbilical vein. If this occurs, the liver and perihepatic lymph nodes are primarily involved. If the lungs become the predominant seat of the tuberculous lesions, the infection may have taken place in two ways. The bacilli may have entered the fetal body by way of the blood stream through the umbilical vein and its branch, the ductus venosus Arantii, which enters the inferior vena cava without passing through the liver. The lungs may also become infected by aspiration of amniotic fluid containing tubercle bacilli originating in placental lesions or in lesions of the endometrium, the latter type of infection occurring after rupture of the membranes. Respiratory movements of the fetus *in utero* occur, as has been repeatedly demonstrated by findings of amniotic material in the lungs of the stillborn or of infants dying shortly after birth.[6]

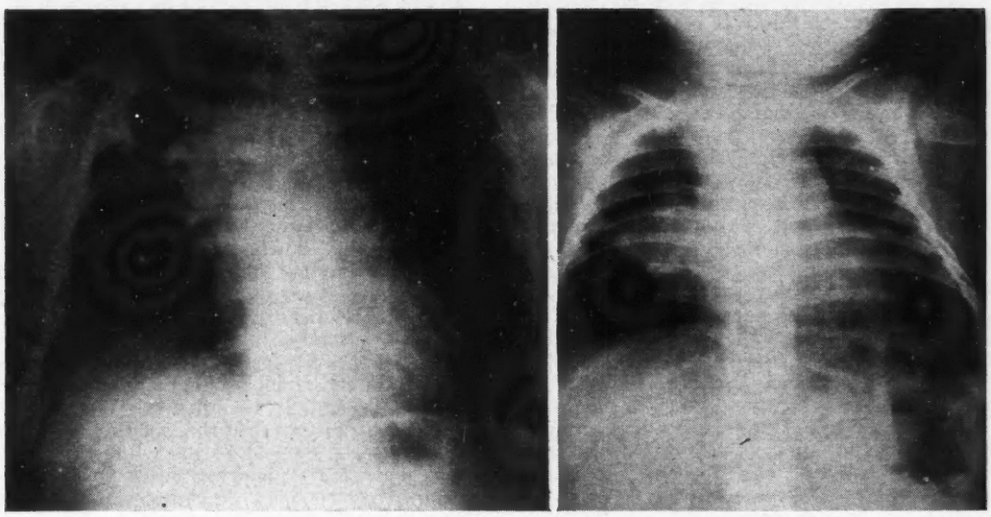

Fig. 1 Fig. 2

Fig. 1.—E.M., age 25. Far advanced pulmonary tuberculosis. Roentgenogram of September 3, 1953, the first month of pregnancy. Fig. 2.—R.M., age 4 months. Primary infection type of pulmonary tuberculosis.

The picture of the disease in the child's lungs varies according to the route of invasion. If the infection takes place via the blood stream, the distribution of the lesions will be miliary. The aspiration of contaminated amniotic fluid will produce multiple foci of pneumonia teeming with tubercle bacilli.[7] It is, however, possible that the latter type of infection may be modified by antibiotic treatment given to the mother during pregnancy, with its weakening influence on the bacilli.

The following case is illustrative of some of the above points, with particular stress on the fact that the child survives and is progressing well.

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TABLE I.

SENSITIVITY TESTS PERFORMED ON TUBERCLE BACILLI OBTAINED FROM THE MOTHER'S SPUTUM IN DECEMBER 1953, THE FOURTH MONTH OF PREGNANCY, SHOWING RESISTANCE TO STREPTOMYCIN, PAS, AND TIBIONE.

Mother sputum cult. Nov. 23, 1953	*Control*	*Streptomycin mcg./ml.* 1	10	50	100	*SM 10γ/ml. INH .5γ/ml. PAS 5 mg/ml.*	*SM 10γ/ml. INH .5γ/ml.*	*PAS 0.5 mg/ml.*	*Isoniazid mcg./ml.* 0.5	1.0	5.0	*Tibione 10γ/ml.*
Lab. No. 4453/53.....	+	+	+	+	+	—	—	+	—	—	—	+

History of the mother: E.M., a 25-year-old Indian woman, was admitted to the Fort William Sanatorium on January 2, 1953, with far advanced active pulmonary tuberculosis. In the spring of 1952 she had had a bad cold, which improved after she received some cough medicine. During treaty time in the summer of 1952 she was x-rayed, but a report of this was not available. Because of continuous cough and feeling of weakness she was finally advised by the public health nurse to enter sanatorium. Her general nutritional status on admission was poor. She had badly infected teeth and gums. The heart was slightly enlarged and there was a systolic murmur present with the maximum point over the mitral area, pulse 88, blood pressure 108/80. Examination of the lungs revealed amphoric breathing over the right upper chest anteriorly and posteriorly, and diffuse fine rales over both lungs. Radiographs showed a large highlight about 10 x 6 cm. in diameter occupying the whole right upper lung field and extending to the third anterior rib. The remainder of both lungs was occupied by moderately dense, nodular shadowing which showed a tendency to conglomeration in the right lower and the left upper lung fields.

The sputum was positive for tubercle bacilli on direct smear and culture, the bacilli being sensitive to streptomycin, para-aminosalicylic acid (PAS) and isoniazid. The urine showed a trace of albumin and occasional white cells; the hæmoglobin content was 14 g. with 3,800,000 erythrocytes, 11,300 white cells, and differential count of 85 neutrophils, 9 lymphocytes, 5 monocytes and 1 eosinophil. The sedimentation rate was 103 mm. in one hour (Westergren).

Treatment, started immediately, consisted of administration of streptomycin 1 g. daily for 10 days, and 1 g. every third day afterwards, concurrently with 12 g. of PAS, daily.

In the following months she showed considerable clinical improvement and the radiograph of her chest on September 3, 1953, showed some decrease in the size of the cavity in the right upper lung field and considerable clearing of the soft, mottled shadowing throughout the lower right and the whole left lung field (Fig. 1). She had gained 24 lb. in weight. However, her sputum remained persistently positive and sensitivity tests of the tubercle bacilli performed in December 1953 showed resistance to streptomycin and PAS (Table I). At that time she had not menstruated for three months. As she had been very irregular before, and in fact had not menstruated since the birth of her last child 20 months previously and only once after admission to sanatorium, she paid no attention to this. However, examination revealed a pregnancy of at least three months. This progressed uneventfully except for hæmoptysis in April 1954, which was soon brought under control. On the evening of June 1, 1954, she went into labour. The pains were very irregular and not sustained, and no progress was made. After 18 hours of labour a Pitocin drip was started, and strong, regular labour pains resulted in normal delivery of a well-developed male infant. The placenta was inspected, and no significant gross abnormality noted. The mother was feeling well and no complications were encountered during the post-partum period. The following months were uneventful, and she is still a patient in our institution at the present time.

History of the child: The baby showed all signs of a full-term normal infant. His weight was 8 lb. 13 oz. He was immediately transferred to the McKellar General Hospital, where he was admitted to the pædiatric ward. Several days later he developed furunculosis, which cleared only slowly with chloramphenicol and local treatment. In the following weeks the child grew normally and nothing of importance happened. On September 7, his temperature rose to 104.3° F. and signs of an upper respiratory infection were present. Cultures of swabs taken from his throat were reported contaminated. The white cell count on September 8 was 9,500, with 72 neutrophils and 28 lymphocytes. On September 11, the child was transferred to the isolation ward. The count on September 12 showed 13,500 white cells with 20 neutrophils and 78 lymphocytes. After treatment with Achromycin (tetracycline) the temperature subsided, and on September 17 he was returned to the pædiatric ward. He continued, however, to have signs of an upper respiratory infection, which was treated with Neosynephrine nose drops and painting of the throat with Mercurochrome. The temperature stayed at 100.5° F. with elevation to 103.3° on September 24 and 26. During these and the following few days he again developed a slight pyodermia, which cleared slowly under local treatment. At the beginning of October it was noted that the child refused food more frequently and showed signs of irritation. On October 12 his temperature rose and gradually reached 104° F. on October 19 and 20. There was evidence of an upper respiratory infection. He was listless and cried frequently. The white cell count on October 15 was 18,450 with 68 neutrophils and 32 lymphocytes. Achromycin was given again. On October 20 a radiograph revealed the presence of a large area of hazy increased density in the right mid-lung field, apparently representing a large patch of pneumonic consolidation. The broncho-vascular markings were accentuated, especially in both lower lung fields. There were no physical signs over the right lung. On October 24 a Mantoux test with old tuberculin 1 in 2,000 was performed for the first time and reported strongly positive. The radiograph was repeated on October 26 and no change was

TABLE II.

TUBERCLE BACILLI FROM CULTURES OF THE GASTRIC WASHINGS OF THE INFANT SHOWING RESISTANCE TO STREPTOMYCIN, PAS, AND TIBIONE.

Baby gastric cult. Nov. 3, 1954	*Control*	*Streptomycin mcg./ml.* 1	10	50	100	*SM 10γ/ml. INH .5γ/ml. PAS .5 mg/ml.*	*SM 10γ/ml. INH .5γ/ml.*	*PAS 0.5 mg/ml.*	*Isoniazid mcg./ml.* 0.5	1.0	5.0	*Tibione 10γ/ml.*	*Viomycin 10γ/ml.*	*Pyrazinamide 10γ/ml.*
Lab. No. 4120/54	+	+	+	+	+	—	—	+	—	—	—	+	+	+

noted in the amount and character of the lesion. After that we were called in for consultation and it was decided that the focus in the right lung represented a primary infection type of pulmonary tuberculosis (Fig. 2). The child was transferred to the pædiatric ward of the Fort William Sanatorium on October 27.

On admission the baby weighed 17¾ lb. and physical examination showed nothing abnormal. The temperature was normal. The laboratory reports revealed a normal urine, gastric washings were negative on direct smear; the culture, however, showed considerable growth of *M. tuberculosis* after five weeks. The result of the sensitivity test of the tubercle bacilli is seen in Table II. Radiographs on admission showed no change from those taken at the General Hospital.

Treatment, begun after several gastric washings had been obtained, consisted of streptomycin 0.5 g. every third day, concurrently with isoniazid, 1 tablet (50 mg.) daily. Up to the present time the child has continued to improve. The last radiograph on January 13, 1955, showed considerable decrease of the lesion in the right mid-lung field.

DISCUSSION

The congenital origin of the infection of the case presented is proven by the following facts:

The mother was treated in this institution for far-advanced pulmonary tuberculosis before and during her entire pregnancy. The child was removed immediately after delivery and admitted to the nursery of the local General Hospital, where he was under the care of a pædiatrician until admission to the sanatorium. Every possibility of exposure during his stay in the General Hospital was excluded. The tuberculous nature of the child's pulmonary disease was proved by repeated positive cultures of tubercle bacilli from the gastric washings and, finally, by the complete identity of the bacilli obtained by culture of the mother's sputum and the child's gastric washings as to sensitivity or resistance to antibiotic and chemotherapeutic drugs.

Infection of the fetus was probably by aspiration of bacilli present in the amniotic fluid, as no miliary distribution in the lungs occurred, and no extrapulmonary disease developed which would have indicated a hæmatogenous infection. Infection probably originated from some tuberculous lesion in the placenta, as there was no evidence of genital tuberculosis in the mother.

The intensive treatment may be responsible for the fact that only one large area of infiltration could be demonstrated in the baby's lungs, instead of the multiple patches of pneumonia usually resulting from aspiration of contaminated amniotic fluid.

SUMMARY

1. Congenital tuberculosis is a rare disease, but a definite clinical entity.

2. Certain criteria must be met to confirm the diagnosis.

3. Tuberculous lesions in the placenta are the most frequent source of infection.

4. There are two routes of invasion: by way of the blood stream and by aspiration of infected amniotic fluid.

5. The form of the lesion in the infant's lungs varies with the mode of infection.

6. Antibiotic treatment of maternal disease before and during pregnancy modifies the nature of the lesions and the course of the disease.

7. A case is presented.

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RINGWORM IN SASKATCHEWAN CAUSED BY TRICHOPHYTON VERRUCOSUM

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A LARGE NUMBER of cattle in Western Canada are infected with ringworm, and many cattle handlers and members of their families contract the infection. One fungus responsible for many such cases is the large-spored ectothrix dermatophyte *Trichophyton verrucosum* Bodin.[1, 2] In the last 20 years this fungus, formerly called *T. faviforme* or *T. discoides*,[3] has been isolated with increasing frequency from human subjects and from cattle and other animals in the United States,[4-7] Canada[1, 2, 8] and England.[9, 10] This increase is due mainly to the improved methods now used for the primary isolation of this slow-growing fungus[6, 11, 12] and to the greater aware-

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ness of the part played by cattle in spreading this infection to humans.

Davidson *et al.* in 1934[1] published the first report of this infection in Western Canada. They recorded 28 cases of suppurative ringworm caused by *T. faviforme* in persons in Manitoba. In 1954 Birt and Wilt[2] reported on 20 more cases in persons in rural Manitoba from which they cultured *T. faviforme*. However, it is in Alberta that the largest number of such cases seem to have been recorded. Thus at the Provincial Laboratory of Public Health, Edmonton, 78 human cases of ringworm caused by *T. verrucosum* were recorded between July 1951 and November 1954 (private communication). Many of the patients were cattle handlers and farmers and members of their families or others residing in rural districts. Cattle and some horses on a number of these farms were known also to be infected with this fungus.

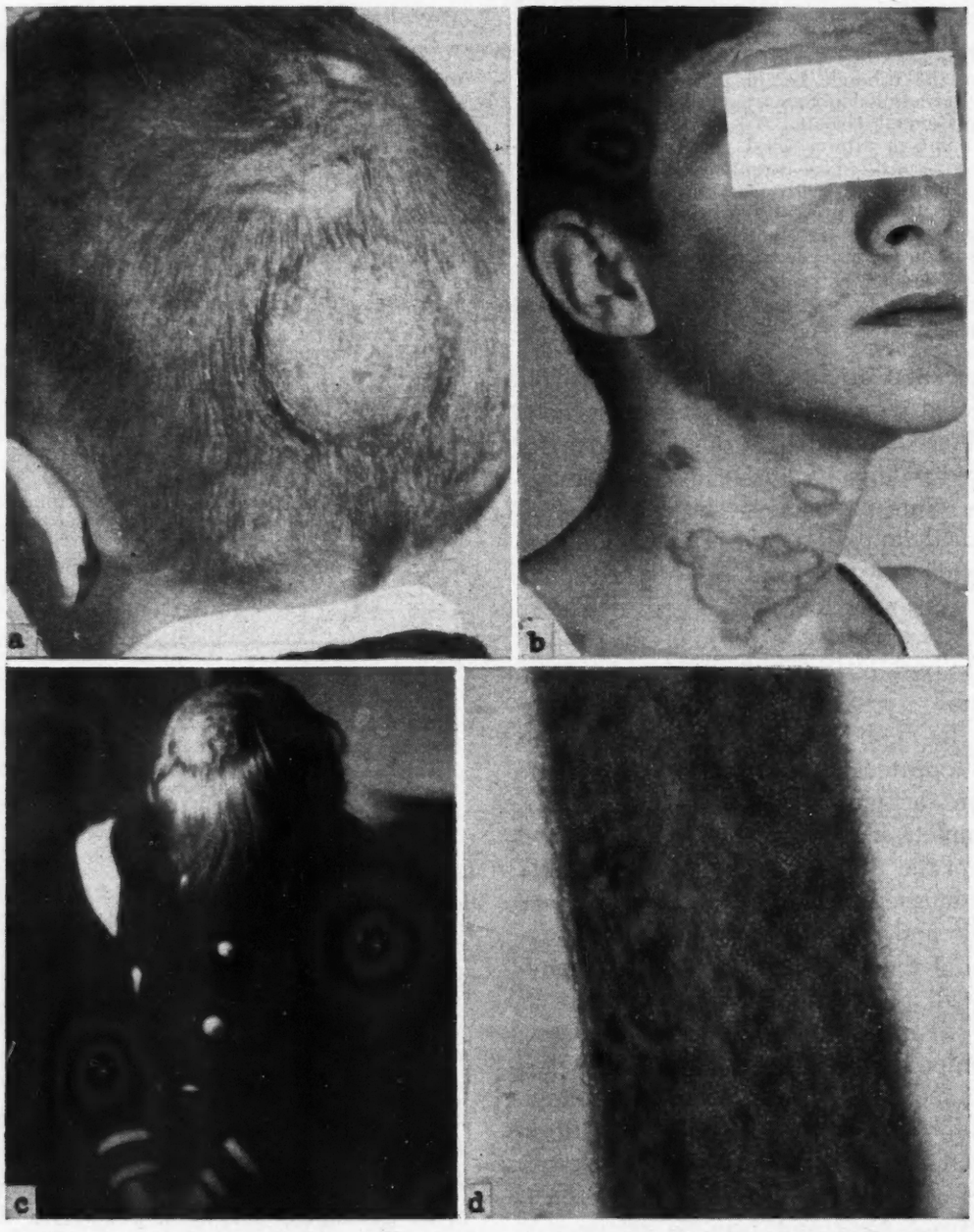

Fig. 1.—(a) Large erythematous sero-purulent plaque on back of head of patient (Case 1). (b) Erythematous concentric papulo-squamous lesions on neck of patient (Case 5). (c) Kerion on scalp of patient (Case 2). (d) Ectothrix involvement of this patient's scalp hairs by spores of *T. verrucosum*.

To this date no reports of this infection in persons living in Saskatchewan have been pub-

lished. Six cases of ringworm caused by *T. verrucosum* were seen between January 26 and March 4, 1955, at the Department of Bacteriology in the Medical College. Four patients reported that cattle were infected with ringworm at the time while a fifth patient reported that cattle had been infected in 1954. These six cases are reported because most of the people in this province live on farms or in rural areas where contact with infected cattle is possible.

CASE 1

M.T., a 5-year-old boy from a farm at Young, Sask. During February 1955 he developed multiple inflamed purulent sores on the back of the head and neck. When we examined him some three weeks after the onset, there were eight erythematous, œdematous, sero-purulent, circumscribed plaques, varying in size from 5 mm. to 5 cm. in diameter (Fig. 1a). Considerable defluvium had occurred from the original and largest plaque. The boy had two pet calves, each of which had active ringworm on the face.

CASE 2

E.S., a 7-year-old boy from a farm at Crystal Springs, Sask. Early in January 1955 he developed a thick, boggy, pustular, inflamed plaque (kerion) on the right parieto-occipital region of the scalp (Fig. 1c). When examined two weeks later, it had attained a size of 6 x 7 cm. Spontaneous epilation had occurred in most of the affected area, and there was marked lymphadenitis of the posterior cervical nodes. The father reported that several of the cattle on the farm had "sores" in 1954, but that no infection was evident during the previous few months.

CASE 3

L.L., a 9-year-old boy from a farm at Horse Head, Sask. Early in January 1955 he developed on the nape of the neck a suppurating sore which gradually enlarged. A week or so later, two similar lesions appeared alongside the original, and another formed on the forehead. He was in hospital for 10 days and received intensive therapy with antibiotics, but the lesions were not influenced. When examined three weeks after the onset, each lesion was a crusted, œdematous plaque of suppurating folliculitis, a typical agminate folliculitis or kerion. The boy had a pet calf with facial sores which were rapidly clearing under application of sulphur in pork lard.

CASE 4

M.H., a 13-year-old boy from the village of Prudhomme, Sask. For about 10 days at the end of February 1955, he had had a slightly itchy, rapidly spreading eruption on the back. Examination on March 3 revealed a very large (15 cm. diameter) lobulated plaque and many discrete and confluent, round and oval, satellite lesions consisting of a pigmented and lichenified central region surrounded by an active erythematous papular, serum-encrusted margin. The affected area included the left lower thoracic-lumbar region and extended a few centimetres across the midline into the right side. There was no suppuration or folliculitis. The left axillary lymph nodes were grossly enlarged, discrete and rubbery, but not tender. The patient had a pet dog which was said to be well. There was no known exposure to animal ringworm.

CASE 5

D.R., a 14-year-old boy from the City of Saskatoon. During the last two weeks of February he had a rapidly spreading eruption on the right side of the neck, composed of several round and oval, single, concentric and confluent, erythematous, papulo-squamous lesions (Fig. 1b). He suspected that the diagnosis was ringworm, and that the infection had been contracted several weeks previously from an infected calf on his uncle's farm.

CASE 6

A.B., a 43-year-old farmer from Fish Creek, Sask. Early in February 1955 he developed an itchy red area on the right upper cheek which slowly extended peripherally until it completely involved both eyelids. On examination on February 28, there was a single large round, sharply circumscribed, erythematous plaque involving the entire right periorbital skin and adjacent upper cheek. This plaque had a papular margin; almost all the eyelashes were set in follicular pustules and could be epilated with ease. Years ago the patient had had a similar self-limited eruption on one forearm. Several of his cattle had active ringworm at the time of each infection.

SUMMARY

1. Six recent cases of cattle ringworm in people in rural Saskatchewan are described.

2. All of these infections were caused by *Trichophyton verrucosum*, which produced suppurative lesions in three of the patients.

3. Cattle in Western Canada are an important source in the spread of this infection to people.

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CANADIAN ASSOCIATION OF OCCUPATIONAL THERAPY

At the 25th Annual Convention of the Canadian Association of Occupational Therapy, to be held in Toronto from October 29 to 31, the banquet speaker will be Edward J. Steiglitz, B.Sc., M.Sc., M.D., F.A.C.P., of Washington, D.C. His topic will be "A Toast to Age". Dr. Steiglitz is consultant in geriatrics for Veterans' Administration, lecturer in industrial medicine at New York University, geriatric consultant at St. Elizabeth Hospital, Washington, and consultant editor of the *Journal of Geriatrics*. Two of the guest speakers will be Dr. John S. Crawford, who will talk on physical and occupational therapy, and Dr. W. E. Boothroyd, who will discuss various aspects of psychiatric and occupational therapy.

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Special Article

A STUDY OF A SAMPLE OF PARTICIPANTS IN THE COMPREHENSIVE MEDICAL CARE PLAN OF PHYSICIANS' SERVICES INC.*

HARDING LERICHE, B.Sc., M.D., Ch.B., M.P.H., F.S.S.† and W. B. STIVER, M.D., D.P.H.,‡ *Toronto*

STATISTICAL METHODS have traditionally been applied by epidemiologists to the study of mass manifestations of infectious disease in groups of populations. These techniques have been used with success also in the study of cancer by McKinnon,[5] in diabetes mellitus by Joslin *et al.*[3] and in child growth and nutrition by Gordon and leRiche.[2] They may also be applied to a study of medical care.

The present study is concerned with a quantitative assessment of medical care in a comprehensive medical care plan. After completion of such quantitative studies, the next step would be the development of measurements of the quality of medical care similar to those carried out by Goldmann and Graham.[1]

It is relatively easy to measure volume of care and frequency of physicians' services to patients, but the analysis of quality is considerably more difficult. For this purpose it will be necessary to undertake assessments of actual practices, which are the field studies of the epidemiologist applied to the phenomenon of medical care. Related to this is also the analysis of the nature of the work of different specialties and the determination of reasonable payment for the various services provided by the medical profession. It is appropriate that in Ontario such studies are being undertaken by an organization set up by the medical profession itself. This indicates that organized medicine is conscious of the need for critical self-examination, a very healthy situation.

The present project is based on a 2% random sample of the comprehensive medical, surgical and obstetrical plan of Physicians' Services Inc. for groups of employed persons. It is a summary of a more extensive monograph which has been presented to the Board of P.S.I.[4] The plan has three different subdivisions: for single persons, for a subscriber and one dependent, and for a subscriber with multiple dependents. The services provided are those which are personally rendered by a physician. The plan does not cover ancillary services such as hospitalization, drugs, dental services, routine health examinations, or mileage. The plan accepts employees without a screening physical examination. All illnesses are covered with the exception of tuberculosis, mental illness, alcoholism or drug addiction when these conditions are treated in a special hospital. There is a 10-month waiting period for obstetrics and a six-month waiting period for tonsillectomy, herniotomy and plastic surgery of the vagina and female perineum. For refractions there is a 10-month waiting period and only one refraction is allowed per agreement year. Radiographic services for diagnostic purposes are limited to $35 per subscriber or dependent per annum, with no limit on those carried out for fractions and dislocations. Subscribers or dependents have a free choice of participating physicians, who sign a contract with the Corporation. Non-participating physicians may also render services, but in this case payments are made directly to the subscriber and not to the physician.

The present study was carried out on 6,047 persons representing 2,331 contracts during 1953. The total number of persons in the comprehensive plan was 313,321, representing 131,120 contracts. At the present time there are somewhat more than 500,000 persons in the

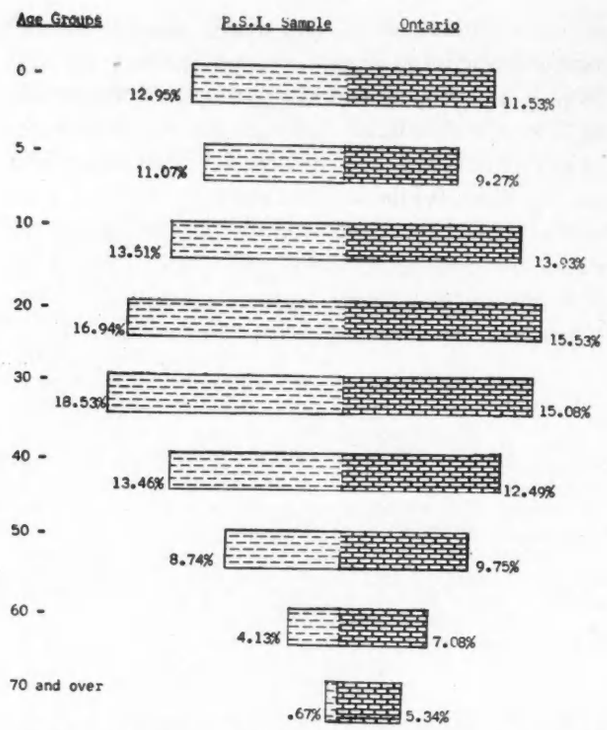

Fig. 1.—Percentage of population, males and females combined, by age group, in the P.S.I. sample and in Ontario, 1953. The P.S.I. sample has a relative excess of population in the age groups under 10 years of age and in the working adult population under the age of 50, compared with Ontario. This sample shows a relatively young population, at present favourable for the operation of a comprehensive medical care plan like P.S.I. If recruitment of young people, especially young adult males, slows down markedly over the years, P.S.I. could be left with the older and more sickly segment of the adult population.

*The voluntary prepaid medical care plan sponsored by the Ontario Medical Association.
†Research Medical Officer, Physicians' Services Inc.
‡Medical Director, Physicians' Services Inc.

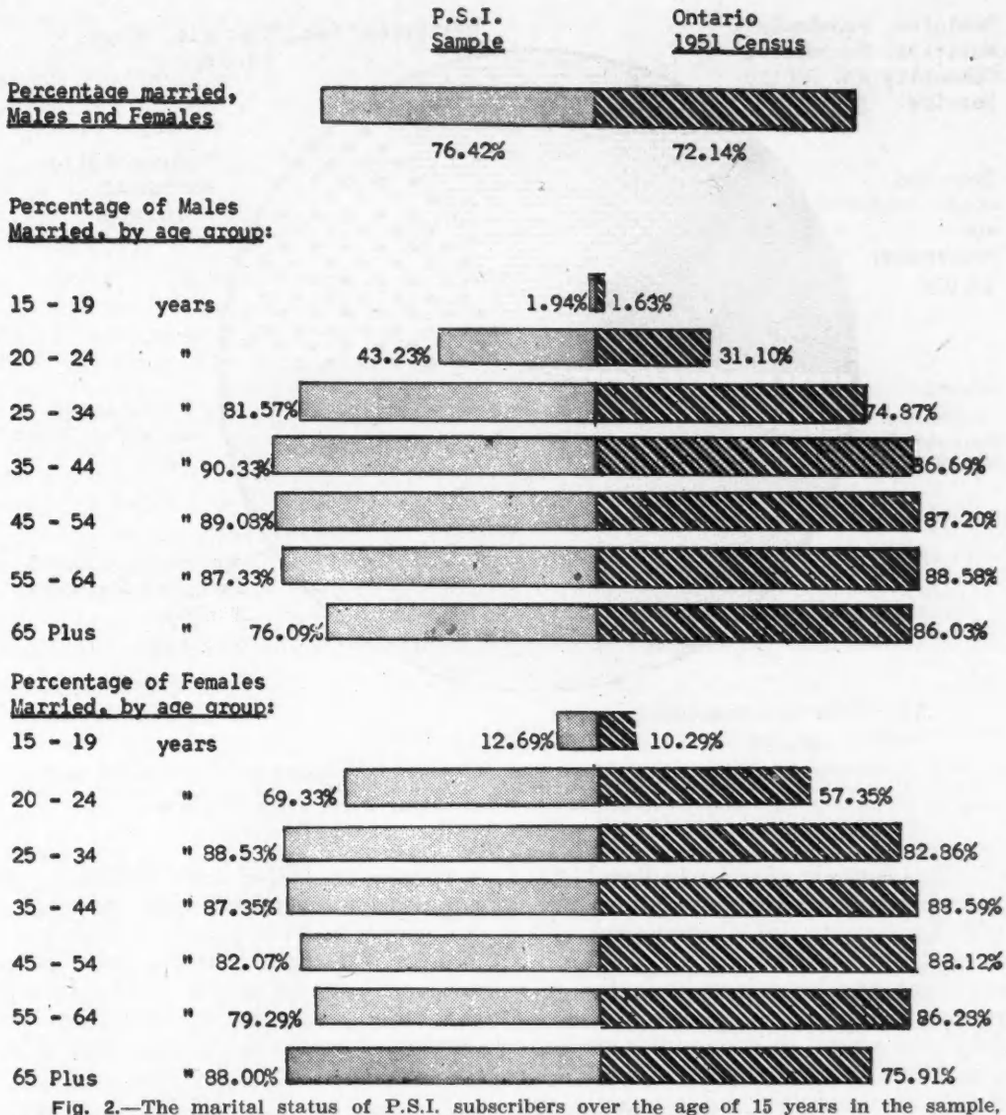

Fig. 2.—The marital status of P.S.I. subscribers over the age of 15 years in the sample, compared with the population of Ontario (1951 census). The P.S.I. sample shows a preponderance of young men and women who have married early, compared with the whole population of Ontario. These are the people who need a prepaid medical care plan, and it appears that P.S.I. is helping to satisfy this need.

comprehensive plan and in the other two limited plans administered by P.S.I. The Comprehensive Plan is by far the largest contract group in P.S.I.

The study will be presented under the following headings: Certain General Characteristics of the Sample Population, Occupational Groupings of Participants, Utilization of Services, Use of General Practitioners and Specialists, Costs, and Control of Volume of Service.

General Characteristics of Sample Population

As shown in Fig. 1 the age distribution of the P.S.I. sample is reasonably close to that of Ontario according to the 1951 census. It is assumed that the age structure of the Ontario population did not change markedly between 1951 and 1953. As may have been expected, the P.S.I. sample has a larger proportion of children and adults of working age than Ontario. It has a markedly lower proportion of persons over the age of 60. P.S.I., therefore, gains by having a younger population with a lower proportion of the diseases of old age.

In Fig. 2 it is shown that the P.S.I. sample has a preponderance of young married men and women, who are the people who need a prepayment plan.

Occupational Groupings

The next question to consider is the proportion of persons in the P.S.I. sample who are dependent upon certain industries. The pie chart (Fig. 3) is calculated in terms of all participants, not in terms of the occupation of the head of the household.

According to the 1951 Census Reports of the Dominion Bureau of Statistics, the following are the 10 leading occupational groups in Ontario, in order of magnitude: (1) Manufacturing and

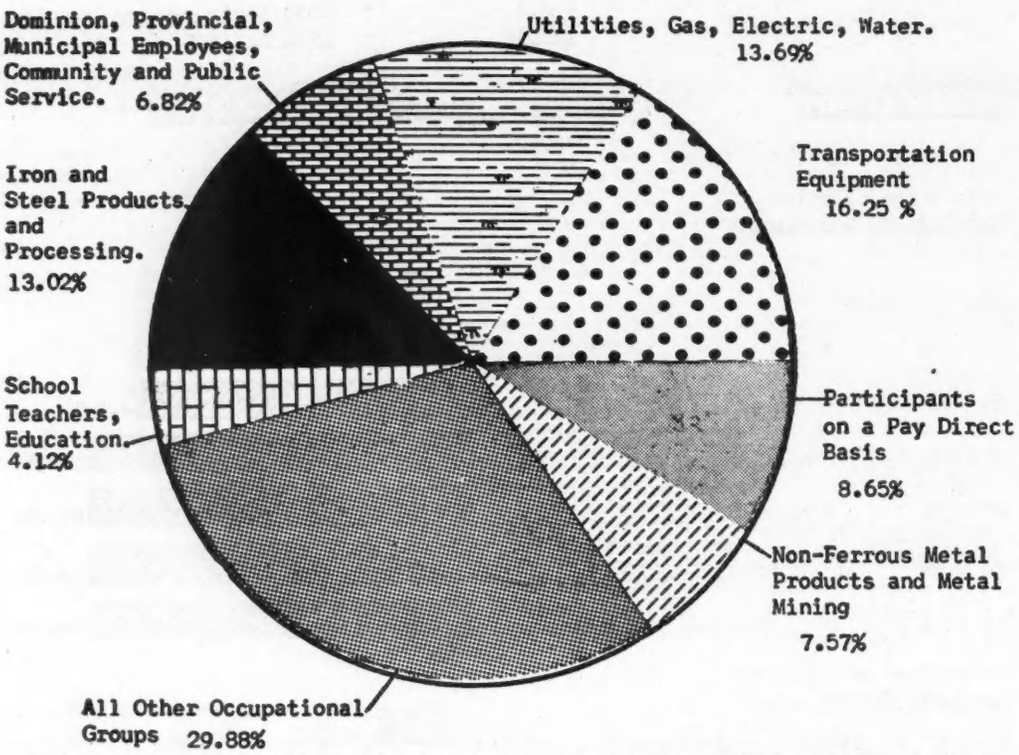

Fig. 3.—Persons in P.S.I. sample dependent upon certain industries. Percentage of all participants. Almost one-third of P.S.I. participants, according to the 1953 sample, are dependent upon the transportation equipment and on the iron and steel processing industries.

mechanical, (2) Clerical, (3) Agricultural, (4) Service, (5) Proprietory and managerial, (6) Professional, (7) Labourers, (8) Commercial, (9) Transportation, (10) Construction.

P.S.I. enrolment has been largely in the industrial groups, in mining, in the utilities like gas, electricity and water, in community service employees, and teachers. In these groups P.S.I. has, of course, also enrolled many people in clerical occupations.

That P.S.I. has not concentrated on proprietory and managerial groups requires no particular comment except the obvious one that these groups probably are not in such great need of prepayment in medical care as are the lower-paid industrial workers. In the manufacturing and industrial groups P.S.I. could make fair headway, but it should be remembered that wage earners in this group numbered 377,000 in 1951. This group would represent, at the maximum, about 900,000 participants. At present P.S.I. has 500,000 participants. Reasonable reserves of subscribers exist for P.S.I. also in the clerical, service, commercial and transportation groups. The agricultural group, a potential 500,000 participants, has not been touched by P.S.I., the main difficulty being that most of these people are self-employed. Nevertheless, it does seem that groups in agricultural co-operatives and other organizations should be considered. It should be possible in this way to obviate or minimize the difficulties of individual collection of premiums.

It may be stated with confidence that P.S.I. is performing a useful social function, especially for young married people in industry. It would appear that there is still a good potential field amongst wage earners for P.S.I. participation and that the possibility of enrolling certain self-employed groups like farmers should be seriously considered.

UTILIZATION OF SERVICES

P.S.I. services are those procedures carried out by physicians for which there is separate payment. For instance, office calls are paid separately. If an office call includes a urinalysis and a hæmoglobin estimation, it is taxed as one office call, not three services. Similarly, an office call accompanied by a therapeutic injection counts as one service. On the other hand, a group of allergy tests is considered a separate service; and when the primary object of a visit to the physician is to receive a therapeutic injection, the injection would constitute a separate service.

In the field of surgery and obstetrics, each major procedure is regarded as one service by P.S.I., irrespective of the number of times the physician may treat or visit the patient for the particular condition. For instance, a normal delivery counts as one service. Actually, it is estimated that on the average physicians will provide five to six prenatal visits, two postnatal hospital visits and at least one postnatal visit six weeks after the confinement. In the case of minor

and major surgery, a similar situation applies. If, therefore, a physician's "service" is regarded as every occasion on which he does something for a patient, the P.S.I. "services" are an underestimate of a doctor's visits.

Furthermore, P.S.I. statistics for medical care are based on "allowed" services, i.e. those procedures for which payment will be made. During 1953, P.S.I. "rendered" services came to 1,050,083 as against 1,046,172 "allowed" services in the "Special Procedures" (Code 1-99) grouping. The number of services which are not allowed is small, but would nevertheless influence average figures. Certain services are not allowed; for instance, if waiting periods have not been fulfilled, or if radiological services are in excess of $35 in any one agreement year, exclusive of x-rays for fractures, dislocations, or therapy.

In the present study, therefore, we shall discuss services in terms of P.S.I. definitions, but an estimate will also be made to give an idea of the total volume of services received by P.S.I. patients, including those individual services and visits which are grouped together as one large procedure such as in surgery.

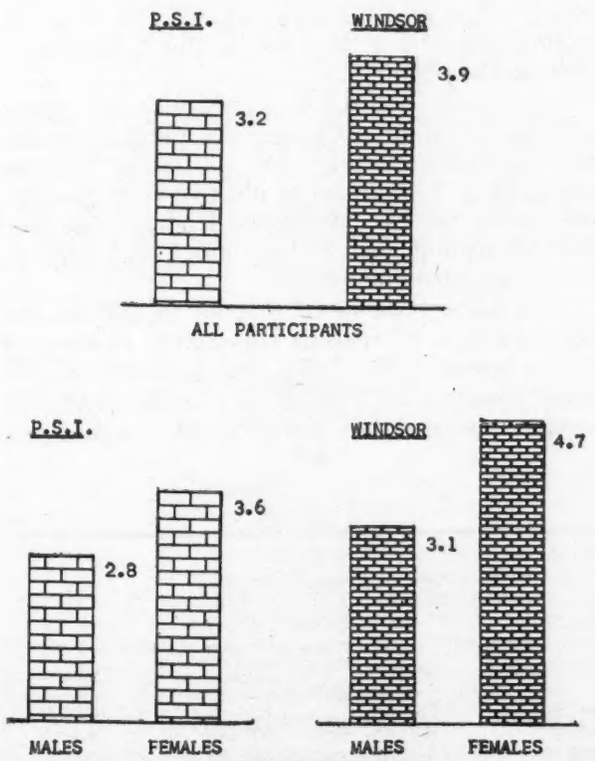

Fig. 4.—Average annual number of services per participant, by sex and age, 1953. P.S.I. and Windsor samples. The average annual calls per person are somewhat lower for the P.S.I. sample than for Windsor. This is probably a real difference, although it should be noted that there are certain small differences in the methods of counting services, between the Windsor and P.S.I. plans. For instance, Windsor counts separate services for each prenatal visit, post-natal visit, and the actual delivery. P.S.I. regards all these procedures as one service. Similarly the care of an abortion is regarded by P.S.I. as one service, while the Windsor plan pays according to the number of calls for this condition. These differences would be of importance only amongst women of childbearing age. Windsor pays for obstetrics on single agreements, but P.S.I. does not.

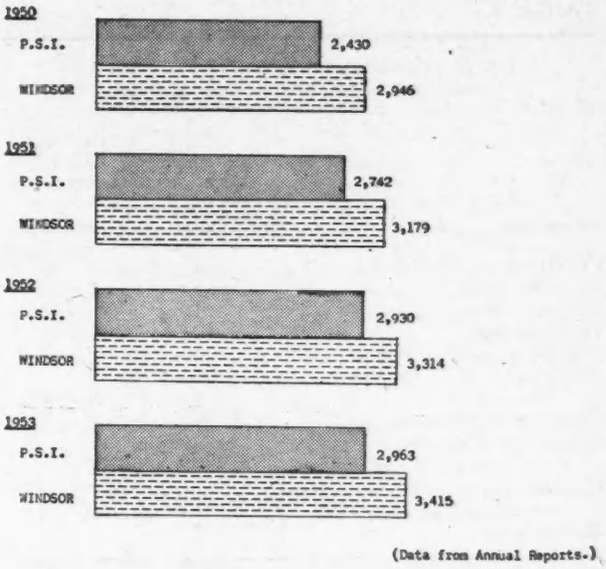

Fig. 5.—All physicians' calls, comparison of Windsor and P.S.I. comprehensive plan. Rates per 1,000 participants per annum. In an attempt to make P.S.I. figures strictly comparable with those of Windsor we have added estimated additional calls to the P.S.I. rate for the obstetrical visits and treatment for abortions. The P.S.I. rate per 1,000 for 1953 would then be 3,178 physicians' calls per 1,000 participants per annum.

As further examples of P.S.I. definitions of services we may mention that a chest fluoroscopy is included with an office call as one procedure. Although incision and drainage of an abscess may entail a number of separate visits by the physician, it is one P.S.I. service. Similarly, refractions, fractures and lacerations are regarded as single P.S.I. procedures.

There are certain small differences between the definitions of procedures in the Windsor* and P.S.I. plans. Under the Windsor plan separate services are counted for each prenatal visit, and the actual delivery and postnatal visits. In abortions the Windsor plan pays for each visit, unlike P.S.I., which pays for only one service. Under the Windsor plan obstetrical services are covered on single agreements.

In Fig. 4 a comparison is made between the P.S.I. and the Windsor prepayment plans. There are certain small differences between methods of computing "services" between the two plans, especially in the field of obstetrics. This is briefly shown in Fig. 5.

In comparing the number of services per participant per annum, in different plans and in different countries, a potent source of misunderstanding is that like is not compared with like. The actual number of physician-patient professional contacts in P.S.I. services is considerably greater than indicated by current statistics, especially in surgical procedures, which are counted as one procedure in P.S.I. accounts, while they in fact represent many hospital or home visits.

*Windsor Medical Services, Windsor, Ontario.

TABLE I.

P.S.I. SERVICES AND ACTUAL TOTAL SERVICES FOR CERTAIN COMMON PROCEDURES

Diagnosis	*Services counted by P.S.I.*	*Services or visits carried out by physician*
Confinement (ordinary)	1	6 - 12
Tonsillectomy	1	3 - 4
Appendectomy	1	3 - 10
Hysterectomy	1	9 - 11
Dilatation and curettage	1	3 - 5
Fracture (Colles, fingers, ribs, toes)	1	2 - 4
Common lacerations	1	2 - 5
Incision and drainage of common abscesses	1	2 - 9
Certain x-rays (gastrointestinal series, gallbladder)	1	2 - 4
Refractions	1	2 - 3

As an illustration, Table I lists some notes that were made on certain procedures in which the physicians specified the number of hospital calls they made. These notes were collected for a short time at the end of 1954 on account cards. A larger series will be collected in order to calculate more stable mean values of "actual" services in surgical and other procedures.

It could be argued that 6 - 12 hospital visits for confinements is excessive, and that it constitutes over-service. Nevertheless, it is possible that patients expect such attention. In addition to hospital visits, obstetrical patients receive about 5-10 prenatal examinations and at least one postnatal visit.

If we apply a conservative estimate of these additional actual services to the total services reported for the complete plan for 1953, we arrive at a figure of at least 4,570 services per 1,000 participants in 1953. This is close to the range of annual services provided in 1953 by the Health Insurance Plan of Greater New York, the Labor Health Institute of St. Louis, Mo., and the Permanente Health Plan.

Reference to Table II will show that rates for physicians' calls have been steadily increasing for the Comprehensive Plan since 1950.

As far as surgery is concerned, the tonsillectomy rate appears to be more or less constant, as does the appendectomy rate. Ordinary confinements showed a marked increase in 1952. This may have been partially due to an increased birth rate, but the most probable explanation is the presence of more married women in the Plan. As would be expected, fractures have maintained a more or less constant rate, but there is a steady climb in surgical procedures, although they appear to have become more stable in 1952 and 1953. There must surely be a limit to necessary surgical procedures in a large population, like that of the P.S.I. Comprehensive Plan. Plewes and Teskey,[6] in a hospital study on appendectomies for the periods 1933-1939, and again during 1946-1952, show an increase of 10% in the number of clinically acute cases not confirmed by pathological section. They feel that this increase is justifiable as it was accompanied by a decrease in the incidence of ruptured appendices.

A comparison of services in prepayment plans and under conditions of private practice would be most illuminating. Of particular interest would be a comparison of elective or reparative surgery in the two situations. It should be possible to arrange such a study amongst people of equivalent economic status.

A problem difficult of solution would be the determination of reasons for increased services in the period 1950—1953. Did patients ask for more care, or did physicians offer additional services because they knew the plan would pay

TABLE II.

PHYSICIANS' SERVICES INC.
ANNUAL RATES PER 1,000 PARTICIPANTS FOR THE COMPREHENSIVE PLAN 1950 - 1953
FOR PHYSICIANS' CALLS AND CERTAIN SURGICAL AND OBSTETRICAL PROCEDURES
TOTAL COMPREHENSIVE PLAN

Physicians' calls	*1950*	*1951*	*1952*	*1953*
Office and well-baby care	1,486.88	1,738.19	1,825.82	1,850.37
Home and night calls	634.72	690.64	679.88	664.64
Hospital calls	308.62	313.57	424.54	448.56
Total	2,430.22	2,742.40	2,930.24	2,963.57
Surgery				
Tonsillectomies, adenoidectomies	16.75	20.89	21.60	18.42
Appendectomies	6.91	6.11	6.03	5.96
Ordinary confinements	10.87	12.65	20.27	19.25
Gynæcological operations	8.44	10.98	12.96	13.01
Fractures	8.26	11.32	11.42	11.13
General/plastic surgery	12.27	15.17	16.62	17.48
Minor surgery	68.77	68.08	91.85	95.48
All surgical procedures	132.27	145.20	180.75	180.73

for such services? We are, of course, assuming that there were no major changes in disease prevalence and incidence during this time.

There can be no doubt that the operation of a plan like P.S.I. does impose changes on the pattern of private practice. We should know the exact nature of these changes. It is inevitable that such a plan will tend to exert pressure on those physicians who have a type of practice which differs markedly from the average, especially if such a practice is more expensive to the plan. We should be able to measure the extent of the constant interaction between plan and physician in order to develop the most efficient service for both participant and physician.

In Fig. 6 the services according to age groups are shown. The higher rates for females from the age of 20 onwards is obvious. Additional care for conditions attendant upon childbirth is to be expected, but a more detailed analysis should be made to discover the reasons for the increase of gynæcological surgery from 8.4 to 13.01 per 1,000 participants between 1950 and 1953 (Fig. 7).

It was possible to obtain an estimate of the number of participants in each age group who were admitted bed patients in a hospital on one or more occasions during 1953. From data provided by the Saskatchewan Hospital Services Plan Report for 1953, it may be calculated that 100 persons in hospital represent 127.2 discharges from hospital during one year. Allowing for a death rate of 2.50% of discharges, 100 persons would represent 129.7 admissions.

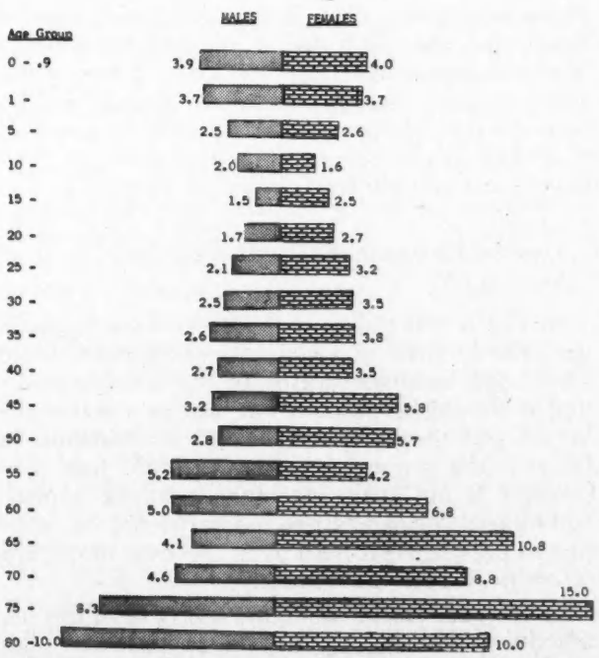

Fig. 6.—P.S.I. 1953 sample. Average annual services per participant by age groups. As in other plans, the higher volume of service for adult females is clearly shown in this sample.

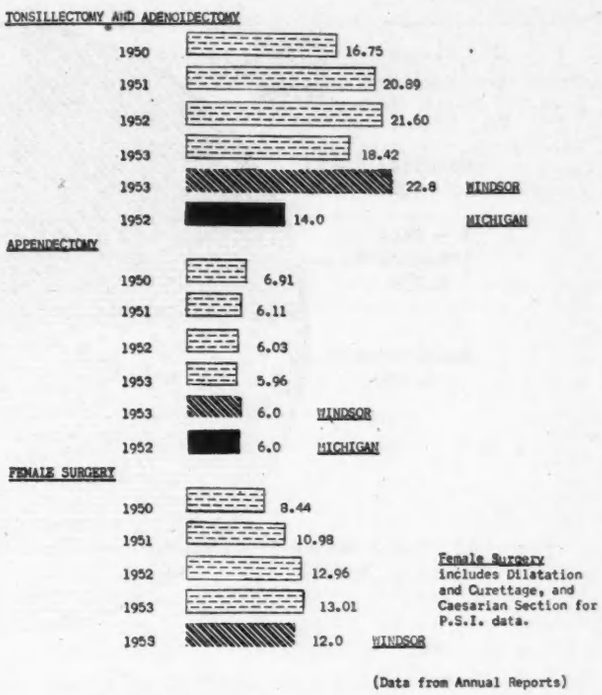

Fig. 7.—Certain surgical procedures in the P.S.I. comprehensive plan, 1950-53. Rates per 1,000 participants. Certain Windsor and Michigan rates for comparison.

From P.S.I. experience, we arrive at an estimate of 151.2 discharges per 1,000 for P.S.I. comprehensive plan participants.

In Ontario, the hospital discharge rate was 123.6 for 1953. This excludes live births in hospital which we estimate as being at least 20 per 1,000 and most probably about 25 per 1,000 in Ontario. The total Ontario hospital discharge rate would, therefore, be in the region of 150 per 1,000 for 1953. Our estimates appear to indicate that P.S.I. participants are not receiving excess service in terms of hospital care.

In contrast to the estimated P.S.I. Sample hospital-discharge rate of 151.2 per 1,000, the Labor Health Institute of St. Louis, Missouri—a prepayment group clinic—experienced a hospital admission rate of only 91 per 1,000 eligible persons in 1952-53. This is a low rate and it may be ascribed to intensive diagnostic services be-

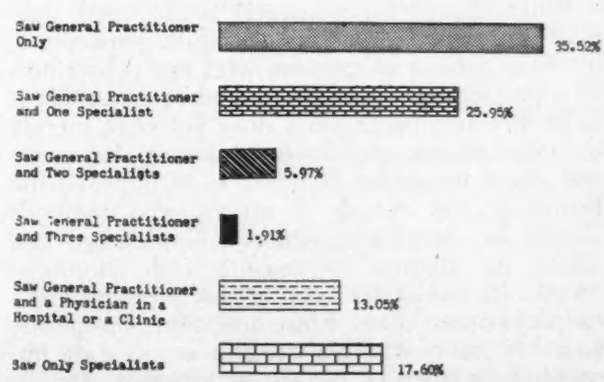

Fig. 8.—P.S.I. 2% sample: utilization of specialists, percentage of participants.

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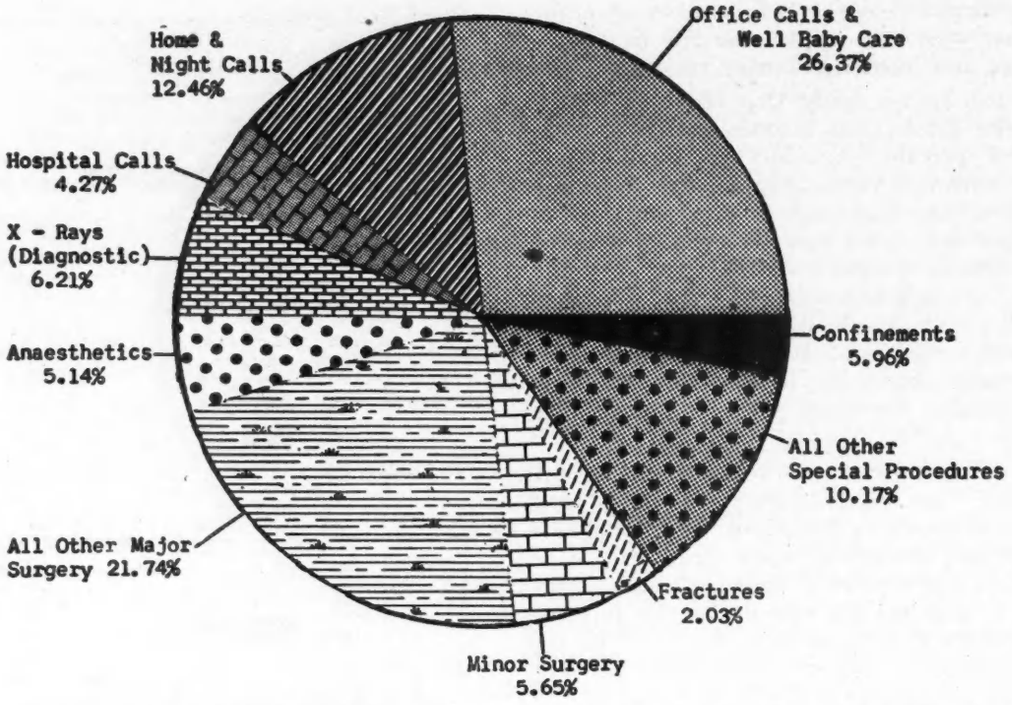

Fig. 9.—The allowed percentage costs of P.S.I. services in the total comprehensive plan. Major categories for 1953.

fore admission to hospital, strict indications for hospital care, and provision of comprehensive clinic medical care before hospitalization.

The development of well-run group practices and clinics can mean a great deal to the future of medical services, both for the physician and the patient. Such clinics, controlled by groups of physicians, can develop efficient diagnostic services which will make it unnecessary for patients to be admitted to hospital merely for diagnostic purposes. Group practices of this type could also carry out clinical preventive services more adequately, thus keeping patients out of expensive hospitals.

On the other hand, from the point of view of a prepayment plan, clinic practice could become needlessly expensive due to excessive use of unnecessary laboratory and other ancillary services. The control of such a situation is one which prepayment plans will increasingly have to face.

What should be measured is the total sickness experience, apart from hospital experience, of these groups of persons who are subscribers to a prepayment plan. Such a plan, especially a voluntary non-profit plan, does not exist merely in order to pay physicians' accounts. Its wider and more important function is to improve the health of the people it serves, and methods should be developed which will measure this effect. An attempt to measure such influences should be undertaken in research programmes on prepayment plans. More and more, the public wants to know whether existing services are improving its state of health, or whether alternative governmental plans will not be better. At the present time, voluntary plans in Canada have every opportunity of trying to work out answers to these questions, but, in view of social and political pressures, they do not have all the time in the world.

A number of interesting facts have emerged from a study of the number of physicians seen by participants during the year. It was found that 30.6% of participants did not consult a physician at any time during the year, and of those who were ill 9 out of 10 received services from not more than two physicians during 1953. This suggests that Ontario participants in the plan do not "shop around", in spite of the fact that they could do so if they wished, as they have a completely free choice of doctor.

USE OF GENERAL PRACTITIONERS AND SPECIALISTS

In Fig. 8 it is shown that 35.5% of participants used the services of a general practitioner, while 17.6% saw only specialists. In the latter connection it should be pointed out that as a fair number of physicians with specialist certification in Ontario do general practice as well, this percentage is not really as high as might appear. In Ontario specialists are not restricted to practice in their special field as is the case in certain other provinces and countries.

In the absence of an actual increase in the fee schedule, increase in costs in a prepayment plan is due to increased use of the plan. This increased use is partially based on what is fashionable or thought to be desirable. For instance, an

increasing number of business executives feel they should have frequent electrocardiograms, often with a blood cholesterol determination. But what they do not realize is that these procedures are not therapeutic (as they perhaps subconsciously hope), and that the tests cannot possibly forestall or predict the date of a particular episode of coronary thrombosis. In many other instances, these and other procedures are used, which are not really part of essential medical care.

Apart from social custom or real need, increased medical care may result from the understandable urge of the subscriber to get value for his money. To counter this it is the obvious duty of the administrators of the plan to see that the participant does not get more than his money's worth, or that the physician does not provide disproportionately frequent service.

COSTS

In Fig. 9 the allowed percentage costs of the P.S.I. comprehensive plan are shown. The importance of office, home and hospital calls—the small, ever-recurring items—is well illustrated. Major surgery plays a somewhat smaller role in the total picture.

The next question which arises is to discover which people are the most expensive to the plan. The first item here is that only 20% of participants in a given year use about 80% of P.S.I. funds while 80% of the participants "make do" on only 20% of the funds.

In more detail, we have shown in Table III a breakdown by age and sex of the high-cost group in the 1953 sample.

Females are the dominant high-cost group. They live longer than males, but their medical expenses are high. Old men, of course, also require frequent medical attention.

CONTROL OF VOLUME OF SERVICE

Statistical methods have been developed which will detect those practices which are markedly different from the average. These averages, including costs per service and costs per sick participant per month, are used as a screening device to select divergent practices, which are then investigated. Quite often, physicians do not know that their practices are markedly different from those of their colleagues. Our averages have been calculated for each of the 54 counties of Ontario, so that in each county a physician is compared with his colleagues in that particular area.

Where it appears that patients are demanding excessive service, letters are written to both patient and physician, and where necessary a consultant is asked to examine the patient. In a few instances P.S.I. has cancelled subscribers' contracts in cases of obvious abuse.

TABLE III.

PHYSICIANS' SERVICES INC.
IN ORDER OF MAGNITUDE, SEX AND AGE GROUPS IN TERMS OF COST (2% SAMPLE). (100 = COST OF MALES UNDER 1 YEAR OF AGE.)

Age and sex group	*Cost factor*
Females 65 and over	215
Females 45 - 49	176
Females 35 - 39	155
Females 60 - 64	153
Males 55 - 59	140
Males 60 - 64	130
Females 30 - 34	129
Females 25 - 29	127
Males 65 and over	118
Females 40 - 44	117
Females 20 - 24	117
Females 50 - 54	111
Females 55 - 59	110
Males under 1 year	100

In our view, it is possible to control costs of a prepayment plan by strict adherence to fee schedules, and by checking excessive use of the service. This is done by statistical controls and by the study of individual practices and patients. When certain physicians habitually give overservice to patients, it has been necessary to pay them according to a formula equivalent to the average costs per patient per month in that particular area. It has seldom been necessary to resort to this particular device, but on occasion its use has been successful.

We feel that investigations could with advantage be undertaken into high- and low-cost groups and into trends in utilization of specialist services. While realizing that it is difficult to control unnecessary utilization, which is subject to pressures other than medical need, we do feel that such control is possible.

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Clinical and Laboratory Notes

MAMMARY CANCER—THE OTHER BREAST*

RAY LAWSON, M.D., *Montreal*

BLOODGOOD in 1921, and George Pack in 1951, advocated removal of the other breast as a prophylactic measure in cases of breast cancer. Pack's argument rests on the following: (1) 7.5% of patients of several series subsequently developed contralateral cancer. (2) The same etiological factors influential in the development of cancer in one breast are probably active in the opposite breast. (3) The same genetic and hormonal factors exist.

The question of whether cancer developing in the second breast is primary or metastatic cannot be answered. Pathologists vary as regards criteria, but all will admit that it is impossible to be dogmatic on that point. While no gross hormonal changes have so far been detected after bilateral mastectomy, there is much evidence to indicate that the breasts play a role in 17-ketosteroid metabolism. It is customary to remove both ovaries if one of them is cancerous, a lesson learned from survival statistics, and this is a far more disturbing type of sexual mutilation than bilateral mastectomy. The ultimate validity of the argument for prophylactic removal of the second breast rests in comparison of survival figures with those in cases of unilateral mastectomy. Unfortunately, no large series of cases have been followed up.

Subsidiary support for the argument may be had by further elucidation of the incidence of gross cancer in the other breast. One hundred consecutive autopsy records of women who had had breast cancer were examined. It was found that at the time of death gross cancer was present in the opposite breast in 13 and that an

TABLE I.

No.	Initial	Case No.	Age	Survival after 1st operation	Survival after 2nd operation	Axillary metast. 1st operation	Axillary metast. 2nd operation	Time between operations
PATIENTS STILL LIVING AFTER BILATERAL MASTECTOMY								
1	McK.	48 - 6979	47	11 years	6 years	R. yes	S. doubtful	5 years
2	S.	44 - 13505	43	14 "	10 "	R. yes	S. benign	4 "
3	V.	48 - 10848	44	6 "	6 "	R. yes	R. elsewhere	3 weeks
4	A.	50 - 9583	46	5 "	4 "	R. no	S. benign	9 months
5	H.	47 - 2218	40	10 "	7 "	R. yes	S. no report	3 years
6	J.	49 - 942	53	7 "	5 "	R. yes	S. no	2 years
7	S.	43 - 14735	35	14 "	12 7/12	R. yes	S. no	17 months
8	M.	50 - 19377	65	11 "	7 "	R. yes	R. yes	4 years
9	H.	52 - 18152	63	22 "	4 "	R. no	S. benign	18 years
10	C.	42 - 5206	46	13 "	5/12	S. no	S. no	7 months
11	B.	50 - 13000	82	6 "	5 2/12	S. yes	S. benign	10 months
12	E.	43 - 14952	43	13 "	10 8/12	R. no	S. benign	2 years 4 mos.
13	W.	44 - 249	47	10 "	10 years	R. no	S. no	3 weeks
14	B.	50 - 11365	47	4 "	4 "	S. no	S. no	same time
15	S.		44	3 "	——	R. no	S. benign	3 years
16	P.	52 - 14183	60	5 "	2 "	R. yes	R. no	3 years
PATIENTS DECEASED AFTER BILATERAL MASTECTOMY								
1	H.	50 - 4201	27	2 8/12	1 6/12	R. yes	S. yes	1 year 2 mos.
2	M.	47 - 8997	46	9 years	2 years	R. yes	S. carcinomatosis	7 years
3	S.	48 - 10812	50	3 "	3 "	S. no	S. benign	same time
4	A.	44 - 3171	63	4 "	2 "	Operation elsewhere, admitted for swollen arm		2 years
5	E.	50 - 12729	41	2 years	1 year	R. yes	S. yes	1 year
6	G.	49 - 709	47	19 "	6 years	R. yes	R. no	13 years
7	J.	46 - 9795	45	5 "	4 9/12	R. no	S. benign	3 mos. Loc. R.
8	K.	53 - 7252	51	7 "	4 6/12	R. yes	S. benign	2 years 6 mos.
9	M.	46 - 18166	50	1 year	1/12	R. yes	S. yes	11 months
10	P.	46 - 2349	50	2 "	9/12	R. yes	S. yes	1 year 3 mos.
11	D.	45 - 4550	41	1 3/12	1 2/12	R. yes	S. yes	1 month
12	R.	42 - 5591	58	15 years	3 years	R. no report	R. yes	12 years
13	R.	43 - 14112	56	4 "	1 year	R. yes	S. yes	3 "
14	W.	44 - 5586	47	9 "	5 "	R. no	S. yes	4 "
15	W.	49 - 2425	62	24 "	2 "	R. bone met.	no report	22 "
16	P.	48 - 3405	70	6 "	5 6/12	R. no	S. benign	6 months

*From the Department of Surgery, Royal Victoria Hospital, Montreal.

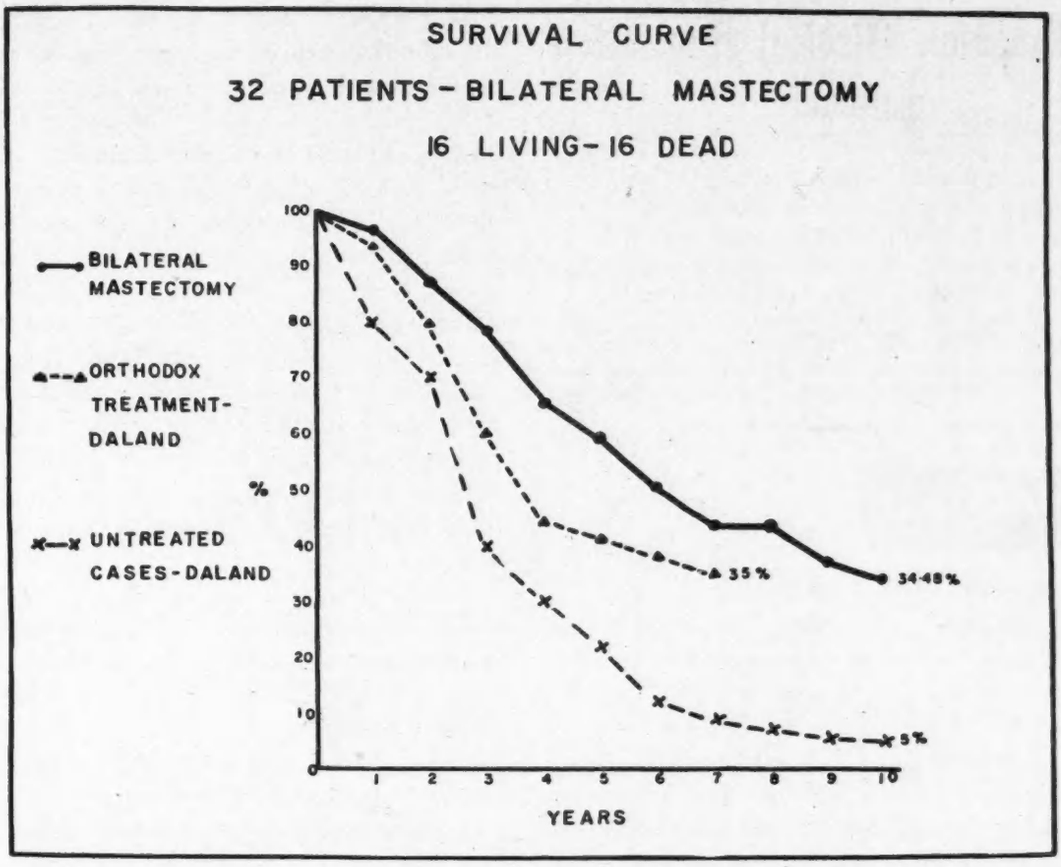

Fig. 1

additional eight had undergone mastectomy because of cancer in the second breast. In this series the state of the other breast was not even mentioned in 22, and as a general rule no histological studies had been made unless gross alterations in structure were suspected. It is therefore reasonable to assume that the incidence of cancer in the second breast is considerably higher than the 21% in our autopsy series.

From the records of a series of 547 patients who had undergone surgery for breast cancer, it was found that both breasts had been removed in 32. Follow-up revealed that 16 were alive and 16 dead (Table I and Fig. 1). The average survival of the 32 patients at the time of follow-up was 8 years 4 months after the first operation. The average survival time of the living patients was 9 years 7½ months and of those deceased, 7 years 1 month. Nineteen of the 32 had gross axillary metastases at the time of operation. Of these, nine are living, with a survival average of 9 years 4 months. The ten who died survived on an average for 7 years 2½ months. Although the series is a small one, the figures are rather striking. There are too many unknown factors involved in this disease to make positive statements. However, another argument in favour of bilateral mastectomy is proposed.

As the average survival time in 19 cases of proven bilateral breast cancer was 7 years 7 months, a figure comparing more than favourably with the expected survival time in unilateral breast cancer, it would appear that the mere presence of the remaining breast may deleteriously influence the course and progress of the metastases. Certainly, removal of the second breast materially alters survival rates.

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FORTHCOMING C.M.A. MEETINGS

1956 Quebec—June 11-15.
1957 Regina—June 17-21.
1958 Halifax—June 15-19.
1959 Edinburgh—July 16-24.
(Conjoint Meeting with B.M.A.)
1960 Banff—June 13-17.

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Editorials

PUBLIC OPINION ON CANCER

On page 639 of this issue we publish an analysis of a survey of opinions held by the Canadian public on cancer. As Dr. Phillips explains, the survey was so designed as to furnish a comparison with a similar survey conducted in Manchester, Salford, and Stockport, England, by Dr. Ralston Paterson and his associates. The object of such exercises is to find out what the general public thinks and knows about cancer, to assess the results of cancer education, and to reorientate the latter if necessary so as to take care of the gaps and errors in public knowledge.

One of the Canadian areas surveyed was the Toronto—Hamilton area, which from the socio-economic point of view is not unlike the area covered by the English study. A comparison of the figures obtained in the two areas, from interviews with women matched as closely as possible for age, marital status and socio-economic grouping, reveals some striking similarities and differences.

Canadian women were much better informed on the relative importance of cancer, tuberculosis and heart disease as killers. Only 4% of the English women correctly placed heart disease as the leading cause of death, as against 43% of Canadians; 52% of English women and 40% of Canadians gave the leading role to cancer, and the English assigned much greater importance to tuberculosis than did the Canadians. A remarkable similarity in designating cancer as the most alarming disease was observed in the two series: 69% and 70% respectively.

Canadians were more optimistic as regards cure. Whereas 50% of the English group thought that cancer was never cured and only 29% had ever heard of anyone being cured, only 25% of Canadians took this gloomy view and 46% had heard of a cure. Canadians were also more sanguine about the value of early treatment, for 80% thought that this increased the chance of cure, as against only 57% of the other group. However, both series held similar views on arrest of spread of cancer by operation. Both groups were reasonably well-orientated on the significance of painless lumps in the breast, but here again the Canadian women were more cancer-conscious; 84% of them, as against only 68% of English women, thought that such a lump was probably associated with cancer or tumour.

On the other hand, knowledge of the possible malignant significance of postmenopausal bleeding was poor in both groups; again Canadian women had much the better score (37% against 19%), though over 90% in both groups would have advised a friend with postmenopausal bleeding to seek medical advice.

A much higher proportion of English women than Canadians said they did not know the first signs of cancer of the breast, womb, stomach or bowels, the largest gap being in the last-named disease (43% English, 11% Canadians); 29% of the English group did not realize the association of the words "tumour" and "cancer"; only 16% of Canadians were in this category.

Asked about the main cause of cancer, Canadians showed themselves better informed, for 38% said it was still unknown (as against 7% of the English), while only 10% attributed it to knocks, bumps or falls (27%, English). Both groups showed a great similarity in the proportions attributing cancer to drinking or immorality.

More Canadian women than English women (60% and 40% respectively) thought that a doctor should tell the patient when he had made a diagnosis of cancer, and slightly more Canadians (71% and 63%) thought that the woman should tell her family.

No doubt both surveys will lead to some modification in lay education programmes; in the meanwhile, it would seem that health education in this field has had a greater impact on the Canadian urban public than on the English public, though the figures show clearly the extent of the job still to be done.

CHEST SURVEYS — AN APPRAISAL

Mass chest x-ray surveys are now about 20 years old. During the latter half of this period, hospital admission x-ray programmes have assumed greater prominence, particularly in view of the increasing trend towards hospital treatment of various illnesses. For the past decade, therefore, mass surveys and hospital admission programmes have been operating concurrently. The decreasing mortality and morbidity from tuberculosis may have resulted in a markedly decreased yield from mass surveys, and it is possible that these have served their educational purposes and should be discontinued. It seems fitting, therefore, that these media of large-scale chest diagnosis be reappraised, evaluated and perhaps set in their proper places.

For an adequate understanding of the problem, it is of some importance that we realize clearly what information both types of survey will provide. In general, the major disease entities detectable by such investigations are pulmonary tuberculosis, pulmonary neoplasms, heart disease and unspecified miscellaneous conditions. There are only three methods by which radiologically discernible chest disease can be diagnosed. A patient with symptoms may present himself to his physician for treatment, and an x-ray of the chest may be ordered. Mass surveys may detect a certain proportion of the latent chest disease present in all populations. Finally, a certain percentage of asymptomatic pulmonary disease may be found by the simple procedure of roentgenological examination of the chest in all patients admitted to hospital. It is abundantly clear that the procedure of referral of symptomatic chest disease by private physicians does not pay dividends from a public health point of view. By the time a patient with chest disease, particularly neoplasm, has begun to have symptoms, the time has usually passed when treatment offers any hope of cure. Furthermore, only a small portion of the population is tapped by this procedure. Mass surveys and hospital admission programmes, therefore, appear to remain our only hope in the early wholesale diagnosis of pulmonary disease.

There seems to be little disagreement that hospital admission programmes are highly valuable, if carried out properly; and there are certain indispensable prerequisites for the satisfactory management of such programmes. For example, it has been found that the location of the photofluorographic unit in or near the admitting office is mandatory. Careful supervision and planning of the programme are of the utmost importance, to ensure that emergency cases that cannot be x-rayed on admission are examined early in their period of hospitalization. Provision must be made for sufficient compensation to the radiologist who interprets the film, to ensure that he treats this work with the care it deserves. Finally, stress must be laid on the fact that even the slightest abnormality in miniature films must be considered sufficient grounds for the exposure of a 14 x 17 inch film. Much of the success of a hospital admission programme depends on the proper use of facilities. For example, small hospitals are advised to use existing x-ray equipment and not to purchase photofluorographic units. From this point of view, it is usually considered that a hospital with 8,000 or more admissions a year has sufficient grounds for the purchase of such a unit. The hospitals that have had the greatest degree of success in their admission programmes are those which have not placed complete dependence on their minifilm unit. These hospitals have concentrated on obtaining a chest film on every admission, even to the point of exposing 14 x 17 inch films when such a procedure is easier for sick patients or taking bedside films in patients who cannot be made ambulatory.

As a result of such programmes, as much as 95% of hospital admissions can be x-rayed, although with poor administration the figure may fall as low as 25%. Such programmes have paid high dividends, not only by detecting incipient chest disease, but also by decreasing almost to zero the incidence of tuberculosis in nurses and other hospital personnel.

Mass surveys are usually conducted either by government departments of health or by semi-private organizations such as tuberculosis associations. In general, such surveys may yield 50 to 100 new cases of active tuberculosis for every 100,000 people examined. They may also be expected to disclose 8 to 10 unsuspected pulmonary neoplasms and 50 to 60 cases of heart disease per 100,000 films exposed. In terms of the funds spent on equipment, materials and staff, this yield is considered in certain quarters to be ridiculously low, and some authorities have advocated their discontinuance. There are, however, certain cogent reasons for proceeding with

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mass surveys, at least for some time to come. As indicated earlier, private referrals and hospital admission programmes involve only a small proportion of the population. Furthermore, mass surveys, particularly in the case of tuberculosis, are the only means of case-finding in rural and other areas where hospital facilities are lacking and the layman's understanding of disease in general is not advanced. As a result of the concerted attack on tuberculosis that has been made during the past 20 years, we are "scraping the bottom of the barrel" in tuberculosis case-finding. It appears essential, therefore, that we make every effort to use the whole population as the reservoir for our case-finding programmes.

In terms of tuberculosis at least, the detection of 50 to 100 new cases per 100,000 examined, while apparently an expensive procedure in equipment and personnel, is still extremely valuable. Most public health authorities feel that there is no expense too great to detect these unsuspecting sufferers from a highly contagious disease. From a monetary standpoint alone, if tuberculosis is not detected until it has entered its advanced stage, the expense incurred by the province or state in curing those affected is certain to be proportionately greater.

A rather different attitude has evolved in connection with population surveys for pulmonary neoplasms. Here it is generally agreed that the yield from mass surveys is too small to be effective. It also seems clear that chest surveys have not influenced and probably will not influence the future mortality from pulmonary neoplasm, possibly because a large proportion of such neoplasms is pre-radiological.

There is as yet little available information as to the efficacy of mass surveys in decreasing the mortality and morbidity from cardiac disease. In all probability it will not be striking, because of the penchant of heart disease to advance steadily before roentgenological signs appear, or never to show such signs at all. Perhaps a more delicate diagnostic device such as the electrocardiogram, or a combination of the x-ray and the electrocardiogram, might be more productive. However, even the electrocardiogram misses a high proportion of cases of heart disease, and the procedure is at present too technical and time-consuming to be practical for mass usage.

It would appear, therefore, at least as it applies to tuberculosis case-finding, that the appropriate procedure should consist of:

(a) An intelligent, persistent, well-administered hospital admission programme, with the use of a photofluorographic unit plus existing facilities for hospitals of 8 to 10 thousand annual admissions or over; and the use of existing facilities alone for hospitals below this admission figure.

(b) Continuation of mass surveys, particularly in schools and in rural areas, so long as they continue to detect an appreciable number of new cases.

S.J.S.

Editorial Comments

SMOKING AND LUNG CANCER

The evidence that cigarette smoking bears a causal relationship to lung cancer has been critically re-examined by Dr. Joseph Berkson of the Mayo Clinic.[1] In the American Cancer Society data studied by Hammond and Horn,[2] current cigarette smokers formed 48.5% in the 50-59 age group and those who reported themselves as having been cigarette smokers at some time in their lives formed 57.4%. The Bureau of Research Information, however, supplied an estimate of about 75% for the latter figure for the general population. This difference along with other pertinent considerations suggests that the American Cancer Society study group was unknowingly weighted with non-smokers of cigarettes. Berkson finds, too, that the age specific death rates of the study group for all causes and for certain specific causes (lung cancer, other cancer, coronary heart disease, other disease) were materially lower than those for the white male population of the United States. The death rates for the non-smokers in the American Cancer Society study were so much lower than those of the United States white male population that, Berkson says, the non-smokers studied were "evidently a lot of phenomenally hardy men", unrepresentative of the general population. Berkson shows how such an unrecognized selection might readily occur and, too, how such a selective factor or factors might readily account for differences between the death rates of smokers and non-smokers and for differences between the rates of smokers of various quantities of cigarettes. He further points out that if a higher death rate for cancer of the lungs in smokers than in non-smokers in the population studied is taken as proof that smoking causes cancer of the lung, then the higher death rates for other cancer and for coronary heart disease and for other causes are similarly proof of the influence of smoking on all or some of these other causes. Thus Berk-

son says, the question is not, "Does cigarette smoking cause cancer of the lungs?" but rather "What disease does cigarette smoking not cause?" But he does not accept any of the differences as proof positive of a causal relationship; they might be attributable to spurious association in the data. He finds, too, that both the retrospective[3] and prospective studies[4] of Doll and Hill are subject to much the same criticism, that some inapparent selection is almost inevitable in such studies (this was recognized as a possibility and considered by Doll and Hill), and that such selection could account for the differences which seemed to be affirmative evidence that cigarette smoking is a cause of lung cancer. However, in spite of the seemingly very cogent argument which Berkson presents, he says, "In reviewing the present paper . . . . I realized that I may have overelaborated some of the points and produced an unbalanced impression. . . . . My thesis is only that it is unwarranted to conclude from them [the various statistical studies] that a meaningful association already has been proved beyond doubt, as some writers have asserted and as appears to be widely accepted in the United States. Much less do I believe that causation has been established. I think that the possibility that selection is the source of the observed association has not been given sufficient weight, and that much more work must be done and time allowed for its evaluation, before a responsible definite opinion can be had as to the precise significance of the findings." He makes a plea, too, for a suitable experimental programme in addition to further statistical study.

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COBALT AND THE THYROID

In January of this year Kriss and his colleagues[1] reported that thyroid hyperplasia and hypothyroidism developed in a number of children given a cobalt-and-iron preparation for sickle-cell anæmia, and suggested that the cobalt was responsible for this. Disagreement has been since expressed in several quarters, and the *Journal of the American Medical Association* has collected in a recent issue four papers, all of which exonerate cobalt as a goitrogenic or antithyroid agent.

In the first, Klinck[2] of Washington, D.C., reports pathological studies of the thyroid in 10 cases of extreme thyroid hyperplasia in childhood. Most of the subjects were infants under six months; five had received cobaltous chloride and five had not. Exactly the same histological picture of hyperplasia was seen in both groups. Holly,[3] from the University of Nebraska, describes studies on 58 pregnant women given cobalt and iron, 20 given cobalt alone, 94 given iron alone and 55 used as controls, in which there were no toxic manifestations due to cobalt. Incidentally, cobalt alone did not prevent the usual fall in hæmoglobin and hæmatocrit values seen in pregnancy. Studies in rats also failed to reveal any effect of cobalt on thyroid function. Holly considers that the results in Kriss's series are attributable to coincidence.

Jaimet and Thode[4] of Hamilton, Ontario, report thyroid function studies on 17 children aged 5-9, given cobalt daily for 10 weeks. They also found a complete lack of antithyroid activity of cobalt, but point out that this does not exclude the possibility either of a rare idiosyncrasy or of a sensitizing action of some concomitant disease such as sickle-cell anæmia. Lastly, Scott and Reilly[5] from the University of California state that, in their experiments on rats, 60 mg. per kg. of cobaltous chloride a day had no appreciable effect on iodine metabolism.

This is reassuring news in view of the widespread use of cobalt as an adjunct to iron salts in treatment of anæmia of prematurity and infancy, and of pregnancy. In the latter instance, cobalt has been shown to produce therapeutic results in the 20% of cases not helped by iron alone, and is therefore a particularly valuable drug.

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LEUKÆMIA AND RADIOTHERAPY

Two papers have appeared this June suggesting a possible association between radiotherapy and subsequent development of leukæmia. The first is a study by Simpson and his colleagues[1] in the University of Rochester, N.Y., of the subsequent fate of 1,400 children whose thymus had been alleged to be enlarged and who had therefore been given local radiotherapy between 1926 and 1951. There was a somewhat alarming incidence of neoplasia in this series, for 17 had later suffered from some malignant condition. Three of the children given a skin dose of less than 200 r developed leukæmia; four of those given more than 200 r developed leukæmia, six developed a cancer of the thyroid and four a cancer elsewhere. In addition, an adenoma of thyroid appeared in six cases. A series of untreated siblings, comparable in number, yielded no cases of leukæmia and only five

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of cancer. Statistically, it appears that the incidence of malignant disease is significantly higher in the treated group than in the siblings or the general population.

The second paper describes an inquiry by Court Brown and Abbatt of London, England, into the subsequent fate of 9,634 patients given x-ray therapy at 37 centres in the United Kingdom for ankylosing spondylitis. Unfortunately only 56% of all such patients could be followed up, but the records show that in no less than 25 a leukæmia developed, at a mean interval of 74 months (range 2-161 months). In 14 cases the leukæmia was a myeloid one, and in 19 it was acute. Calculation shows that the incidence of deaths from leukæmia in this series was from 5 to 10 times that in the general population. (The lower figure is based on the assumption that none of the untraced patients developed leukæmia.) The incidence was higher when more than one course of x-rays had been given, and then reached nine times the expected rate for the general population.

Both sets of authors point out the possibility that either ankylosing spondylitis or thymic enlargement may itself be associated with leukæmia (in 4 cases, the spondylitis and leukæmia did actually coincide), but the increased incidence of leukæmia with increase in irradiation suggests the alternative explanation, that the x-rays were responsible for the neoplasia. This, of course, is in line with previous findings of an increase in leukæmia in survivors of atomic explosions, and of an increase in leukæmia among radiologists. Brown and Abbatt sum up their views as follows:

"In spite of these findings it would be wrong to withhold x-ray treatment from those suffering from ankylosing spondylitis. It is common knowledge that the life expectancy of many of these patients is reduced by their disability, and most authorities agree that radiotherapy has in many instances a beneficial effect. What is certain, however, is that no-one should be treated with x-rays unless the diagnosis is clearly established, and that a second course of x-ray treatment should not be given unless absolutely necessary."

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STUDYING THE PORTAL CIRCULATION

The biliary tract and the portal circulation have lately been intensively studied, and aspects of their dynamics hitherto unknown and often unsuspected are coming to light. Thanks to the new contrast agents such as Cholografin, investigation of bile-duct function is at last giving results without recourse to laparotomy. Similarly, the portal venous system is becoming accessible to study without surgical intervention.

The diagnosis of portal hypertension, like that of arterial hypertension, is best made by measurement of venous pressure rather than by inference from clinical signs and symptoms. Two recent papers suggest ways in which such measurement can be done. Bierman *et al.* (*J.A.M.A.*, 158: 1331, 1955) from California describe a technique of trans-hepatic portal venipuncture and catheterization of the portal and hepatic veins which they have now used 144 times. They introduce a No. 16-18 needle 15 cm. long with a distal side-opening and an obturator at a point 1 cm. below the xiphoid process and 1 cm. to the right of the midline, 5 to 10 degrees superiorly to the horizontal and at an angle of 20 to 40 degrees with the sagittal plane, to a depth of 12 cm., and in this way enter one of the major portal tributaries. Through the needle, the portal venous pressure may be measured directly, the vein may be catheterized, or the portal venous tract may be injected with a venographic contrast agent. The method failed in only nine out of 73 patients, and in some cases both the hepatic and the portal veins were catheterized.

The hydrostatic pressure in the portal vein of normal persons was shown by this method to fluctuate with the respiratory excursions but rarely to exceed 10 cm. of water. In portal cirrhosis or intrahepatic portal obstruction, however, it rose to 22 cm. H_2O. In addition, venography revealed differences in venous pattern between normal and cirrhotic livers and livers containing metastases from malignant tumours.

Lemaire and Housset (*Presse Méd.*, 63: 1064, 1955) suggest a simpler technique for measuring portal venous pressure. They merely introduce a needle of 1.7 mm. diameter into the liver as for biopsy, to a depth of 1-2 cm. They then withdraw the stylet, attach the needle to an anæroid manometer, and record the intrahepatic pressure, which in their opinion approximates to the portal vein pressure. They give figures in agreement with those of the American observers: 7-13 cm. of water in normal subjects, and 27-45 cm. in cirrhotics. By a similar method they recorded the intrasplenic pressure, and found it similar to the intrahepatic except in portal block outside the liver.

Lemaire and Housset also review indirect methods of measuring portal pressure, as by measuring pressure inside an œsophageal varix or in an umbilical vein. Both the above are quite inaccurate. Catheterization of a hepatic vein gives a better though somewhat low measure. These authors suggest that although the normal average portal pressure is 10-12 cm. of water, pressures of up to 20 cm. may be regarded as physiological.

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PUBLIC RELATIONS FORUM

Conducted by L. W. HOLMES,
Assistant Secretary, C.M.A.

III. AMBASSADORS OF GOODWILL

"HOSTESS, nurse, receptionist, orderly, telephone operator, secretary, bookkeeper, historian, file clerk, typist, practical psychologist, all-round technician and diplomat extraordinary—the doctor's aide has quite a job! In all the world of business it would be hard to find a feminine occupation that calls for greater diversity of talent. Certainly there is none in which the appointee can more crucially affect—for better or worse—the success, happiness and popular esteem of her boss."

James E. Bryan, in his book *Public Relations in Medical Practice,* may be using extravagant words to emphasize the importance of the doctor's assistant, but he does not write in hyperbole. The "Gal Friday" in the doctor's office is probably the key person in shaping the patient's opinion of her employer, his office and practice. Thoughtlessness or carelessness can spell doom for his "personal" public relations. On the other hand, the neat, attractive, pleasant and efficient aide is "good medicine" for any patient, and a PR asset to be prized.

What are the characteristics which the ideal office assistant should possess? Naturally she should have the education and training adequate for the position she is expected to fill. But, additionally, as the doctor's goodwill ambassador she should have a good personality, combining friendliness, courtesy, graciousness and sympathy. She should be cheerful, tactful, patient and levelheaded.

Certainly few such paragons exist. However, these are qualifications for which the doctor should look when hiring office personnel. Moreover, persuasion and guidance may help develop many of these virtues in the willing assistant. The doctor's attention to his assistant's training will pay rich rewards in more human and more harmonious doctor-patient relationships.

On what should the doctor insist when detailing the duties and responsibilities of his office assistant? A group of doctors, conscious of the public relations value of the office aide, suggest she follow these basic practices of good PR:

1. She should greet each patient with warmth. Patients have a right to expect courtesy in the doctor's office; friendliness should be an added ingredient. Patients are worried and frequently in discomfort. The receptionist's warm, human understanding will do much to put them at ease.

2. She should attempt to give the patient some idea of how long he will have to wait to see the doctor. If the patient shows signs of restlessness, the assistant can frequently overcome the irritation of waiting by showing him a little personal attention.

3. She should develop good telephone habits. The telephone is an emissary of goodwill and good public relations. The doctor should observe his employee's telephone tactics and insist that such practices as mumbling, brusqueness, or slamming the receiver be eliminated.

4. She should screen carefully those demanding of the doctor's time. But she must be informed what non-patient callers—the detail men, the relatives, the friends, the salesmen—the doctor will see. Within this framework of instruction she can then shield the doctor from unnecessary timewasters.

5. If the doctor is so disposed, he may use his office assistant to broach the subject of payment of accounts. She may suggest to the incoming patient that he bring up the matter of payment with the doctor. This lifts the responsibility from the shoulders of the doctor who is reluctant to introduce business matters during examination or treatment. Or she may politely ask the patient, as he departs, how he would like to settle his account.

6. The office assistant's obligation to the patient includes a friendly and appropriate farewell.

One thing on which the doctor must insist is secrecy. It is not unknown for doctors' assistants to discuss "the day at the office," relating anecdotes complete with patients' names. Next to mediocre medical practice there is probably no more effective way to keep patients from the office than to employ an indiscreet assistant.

An efficient assistant can save the doctor time and money; she can win him friends. But she must be thoroughly trained. Her duties must be outlined clearly and specifically—but she must be given time to learn. The importance of attention to detail must be impressed upon her, and she must be warned that mistakes in a doctor's office can be tragic. Advance agreements on just what procedures are to be followed in specific situations should be worked out.

The doctor, as an employer, has responsibilities to the office assistant. Good assistants deserve good wages. And appreciation for their loyalty should be shown in tangible ways.

A loyal, personable and well-trained assistant can be one of the doctor's biggest public relations assets. It's just good sense and sound business practice to capitalize this resource.

EMERGENCY CALL SYSTEMS

More and more medical societies in Canada are turning their attention to the elimination of a common source of public criticism—inability to get a doctor in emergencies. One of the vehicles being used is the Emergency Call System whereby a central telephone exchange provides doctors from a roster when emergency calls are received.

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In the August 31 issue of *The Montreal Star* two articles describe the call system operated by the Toronto Academy of Medicine, and the provision of emergency medical services in the city of Montreal. These articles also illustrate how the Emergency Call System may be publicized.

Interested readers may obtain copies of these two articles by writing to Association offices, 244 St. George Street, Toronto 5, Ontario.

GENERAL PRACTICE

GENERAL PRACTITIONER RESEARCH

THE FAMILY DOCTOR is in an advantageous position to contribute to medical research. He sees the beginnings of disease and treats many conditions of considerable significance that rarely appear in hospitals. He knows the family background and many of the hereditary factors playing a part in the illness of his patients. He is a most important member of the medical team in terms of continuing medical care, particularly of chronic diseases and the ailments of the aged.

Though these statements accurately indicate some of his field of influence, research by general physicians has become unduly limited. Several reasons have been advanced for this. One is that little attempt has been made in his undergraduate training to show any need for research in general practice. Its possibilities were not pointed out. Another factor is that such studies today seem to require direction and guidance, particularly when so much of it can become part of a group research scheme, with co-operative efforts by a number of workers.

The College of General Practitioners of the United Kingdom has opened up this field and is pioneering in it. It is developing a unique research organization dedicated to group research and collective investigation. It is demonstrating how the general physician may unearth new knowledge of disease and, as a side-effect, how this may improve the quality of general medical care. The latter is one of the greatest benefits of planned group research because the doctor who participates in such projects has greater zest for his daily work.

The machinery adopted by the College of General Practitioners of the United Kingdom for promoting research is briefly as follows:

In 1953, they invited those members interested in research to submit their names to the Research Committee. This became the Research Register which now contains some 450 names. These were quickly linked into groups with similar interests.

They were kept informed by newsletters of the progress being made. The first five newsletters were confidential and contained reports of original clinical work. They were intended to estimate and measure the amount of clinical research being carried out. The College was surprised at how much excellent work was being done. The latest newsletters have been printed and a copy of number 8 has just been received. We would like to quote rather freely from it as it does reveal the interesting manner in which this is developing.

Newsletter Number 8 contains reports on:

1. Epidemic winter vomiting. This is a detailed report and is described as an experiment in collective epidemiology in which 159 general practitioners took part. This condition is a disease of unknown cause, though probably of virus origin, and of sporadic and epidemic distribution. The experiment has more clearly defined its clinical features.

2. Glandular fever, or infectious mononucleosis as we know it. Thirty-one doctors contributed to this study. It is shown that this disease is by no means rare and often presents a difficult diagnostic problem.

3. Infectious hepatitis. This survey showed that there were no epidemics in the U.K. this year, and therefore no new or startling results.

Another interesting project is being undertaken with a rather different approach. This is a study of asthma in children. The Minister of Health was approached and stated that he wanted to know:

1. How many children between the ages of 5 and 15 recover spontaneously from asthma?
2. What happens to those who do not recover?
3. What forms of treatment are valuable in combating this condition?
4. What can the Ministry of Health do to help?
5. Is open-air school treatment a good thing?
6. Should there be more open air schools?
7. Should children be sent to Switzerland or is there a less expensive way of achieving the same results?

Thirty-six members of the Research Register have indicated that they will help in this study. A short bibliography of articles on this subject is being prepared, and questionnaires will be mailed to participants. One pædiatrician stated that the data obtained must include: (1) A family history of allergic conditions. (2) The infant feeding history. (3) Frequent observations. The child must be seen at frequent intervals, maybe monthly, but certainly not less than every three months. He must be seen at regular intervals both during and between attacks. The study must continue at this intensity for not less than five years and there must be a 100% follow-

up. This prolonged observation should be possible in general practice.

This will indicate somewhat the scope and method of procedure adopted by the College of General Practitioners of the United Kingdom in developing its programme of research in general practice. The College of General Practice of Canada is convinced of the great value of a well-planned programme, and is persuaded that it could add to our knowledge of disease. Also, it is an educational tool for the participating doctor, in that it demands a more careful study of some of the problems he is handling. It becomes a discipline for him, with its requirements of close observation and honesty.

This programme of the College of General Practitioners of the United Kingdom has stimulated and encouraged us to enter this field. In June of this year, Dr. M. E. W. Gooderham of Don Mills, Ontario, was asked to chair a committee to outline for us a plan whereby we may make a beginning. The details of this and of how you may help us by participating in it will be given in an early issue of this Journal.

POSTGRADUATE COURSES

St. Paul's Hospital, Vancouver, B.C.: Oct. 27-29, 1955.

Vancouver General Hospital, Vancouver, B.C.: Medicine, Nov. 16-18, 1955; Pædiatrics, Dec. 7-9, 1955; Surgery, Feb. 6-8, 1956; Anæsthesiology, Feb. 20-22, 1956; Obstetrics and Gynæcology, Mar. 26-28, 1956.

Interstate Post-Graduate Association of North America, Madison, Wisconsin: Nov. 14-17, 1955, $10.

University of Minnesota Centre for Continuation Study, Minneapolis: Techniques in General Practice, Oct. 20-22, 1955, $25, Fractures for General Physicians, Nov. 21-23, 1955, $35.

Chicago Medical Society, 86 E. Randolph Street, Chicago 1: Basic Principles and Recent Developments in Pædiatrics, Oct. 17-21, 1955, $75; Basic Principles and Recent Developments in Obstetrics and Gynæcology, Oct. 24-28, 1955, $75.

Cook County Graduate School of Medicine, 707 S. Wood Street, Chicago 12: Gynæcology, Nov. 28, 1955, two weeks, $150; Feb. 13, 1956, two weeks, $150. Obstetrics, Nov. 7, 1955, two weeks, $150; Feb. 27, 1956, two weeks, $150.

University of Buffalo School of Medicine: Recent Advances in Chest Disease, Nov. 17, 1955, $15; Infectious Diseases, Dec. 7, 1955, $15; Arthritis, Jan. 19, 1956, $15; Endocrine Disease, Feb. 9, 1956, $15; Hæmatology, Feb. 29, 1956, $15; Obstetrics, limited to 16, Mar. 7-8, 1956, $30; Psychiatric Problems in General Practice, limited to 16, Mar. 29, 1956, $15; Anæsthesia, Practical Course, limited to 10, Mar. 23-28, 1956, $75.

Sheraton-Cadillac Hotel, Detroit: Annual Fall Postgraduate Clinic, Nov. 9-10, 1955; Office Procedures for the General Physician, Feb. 1, 1956.

Royal Victoria Hospital, Montreal 2: Refresher Course for General Practitioners, Nov. 21-26, 1955, $50.

New York Polyclinic Medical School, 345 W. 50th Street, New York 19: Courses may be arranged for individual doctors in such general subjects as Clinical Gynæcology, General Medicine, Clinical and Office Obstetrics and Pædiatrics; also in particular subjects such as arthritis.

ABSTRACTS *from current literature*

MEDICINE

Role of Auscultation in Differentiation of Fallot's Tetralogy from Severe Pulmonary Stenosis with Intact Ventricular Septum and Right-to-Left Interatrial Shunt.

Vogelpoel, L., and Schrire, V.: Circulation, 11: 714, 1955.

The differentiation of Fallot's tetralogy from severe pulmonary stenosis with intact ventricular septum and reversed interatrial shunt is important because the surgical treatment is different. While the diagnosis can generally be made on clinical grounds alone, it is usually necessary to confirm the diagnosis by special investigations.

A clinical and phonocardiographic study of the heart sounds and murmurs has been made in six cases of severe pulmonary stenosis with intact septum and in 18 cases of Fallot's tetralogy.

A striking difference in the behaviour of the systolic murmur at the site of maximal intensity was found in the two conditions, if attention was directed to the duration of the systolic murmur in relation to the second heart sound and to the position in systole of its maximal intensity. In Fallot's tetralogy the systolic murmur, however soft or loud, starts soon after the first sound, reaches maximal intensity by mid-systole and then diminishes markedly, usually ending before the single loud, often palpable, aortic component of the second sound. By contrast, in severe pulmonary stenosis with intact ventricular septum, the systolic murmur is so prolonged that it extends beyond and drowns the normal aortic component of the very widely split second sound. It stops before the delayed, diminutive pulmonary component which may or may not be audible.

This significant difference in the systolic murmur so clearly shown by phonocardiography is readily appreciated by the ear and affords a new simple bedside method of diagnosis.

Phonocardiographic studies revealed further points of interest. In severe pulmonary stenosis with intact septum, the second heart sound is very widely split, because a diminutive pulmonary second sound is widely separated from the normal aortic component. In Fallot's tetralogy the second sound is usually single because the loud aortic sound is followed by an inaudible pul-

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monary sound. However, if the pulmonary artery pressure is sufficiently high, this delayed pulmonary second sound becomes recordable and even audible. The mechanism underlying these findings is fully discussed.

A presystolic murmur loudest in the left parasternal region was heard in a case of severe pulmonary stenosis with intact ventricular septum and reversed interauricular shunt. It was attributed to flow through the atrial septum or the stenosed pulmonary valve during atrial systole.

A loud atrial sound was heard in three cases of severe pulmonary stenosis with intact septum but not in Fallot's tetralogy.

In four severe cases of Fallot's tetralogy in which the murmur was not intense, an early systolic sound was heard which caused "wide splitting" of the first sound. In two cases of severe pulmonary stenosis with intact ventricular septum, close splitting of the first sound was heard with an intense clicking second component. The mechanism underlying these findings is discussed.

S. J. SHANE

Electrocardiographic Pattern of Right Ventricular Hypertrophy in Mitral Valve Disease.

SCOTT, R. C. *et al.*: CIRCULATION, 11: 761, 1955.

The electrocardiographic patterns encountered in 32 patients with mitral valve disease were compared with the resting pulmonary artery pressures, with the pulmonary resistances and with the mitral valve areas.

Seventeen patients had pure mitral stenosis. Nine of these showed the pattern of right ventricular hypertrophy and two showed incomplete right bundle branch block. Eight of the nine with hypertrophy and one with incomplete right bundle branch block had total pulmonary resistances in excess of 1,000 dynes per second per cm.

In pure mitral stenosis if the total pulmonary resistance is 1,000 dynes per second per cm. or greater, the electrocardiogram will usually (although not invariably) show the pattern of either right ventricular hypertrophy or incomplete right bundle branch block.

If mitral insufficiency and/or aortic valve lesions coexist with mitral stenosis, the total pulmonary resistance may exceed the level of 1,000 dynes per second per cm. many times without the development of the pattern of right ventricular hypertrophy.

When the electrocardiographic pattern of right ventricular hypertrophy is encountered in mitral valve disease the following inferences may be drawn: (a) The patient does not necessarily have pure mitral stenosis although it is probably the predominant lesion. (b) The total pulmonary resistance is probably 1,000 dynes per second per cm. or greater.

S. J. SHANE

The Electrocardiographic Pattern of Right Ventricular Hypertrophy in Chronic Cor Pulmonale.

SCOTT, R. C. *et al.*: CIRCULATION, 11: 927, 1955.

Twenty-eight patients with pulmonary hypertension secondary to chronic lung disease have been studied by cardiac catheterization.

Thirteen patients did not show the electrocardiographic pattern of either right ventricular hypertrophy, or right bundle branch block; 15 patients showed right ventricular hypertrophy and/or right bundle branch block (complete or incomplete).

A statistically significant difference was demonstrated between the means of these two groups for the following physiological measurements: mean pulmonary artery pressure, total pulmonary resistance, arterial oxygen saturation, and right ventricular work.

All cases except one with the pattern of right ventricular hypertrophy had a mean pulmonary artery pressure greater than 30 mm. Hg.

All cases whose total pulmonary resistance exceeded 750 dynes/second/cm. showed the electrocardiographic pattern of right ventricular hypertrophy or right bundle branch block (complete or incomplete).

The development of the pattern of right ventricular hypertrophy in patients with chronic cor pulmonale usually indicates an advanced state of the disease.

S. J. SHANE

Angina Pectoris Induced by Fat Ingestion in Patients with Coronary Heart Disease.

KUO, P. T. AND JOYNER, C. R. JR.: *J. A. M. A.*, 158: 1008, 1955.

The observation that in dogs a slow intravenous injection of a fat emulsion preparation caused a drop in the oxygen tension readings and an apparent decrease in the amplitude of myocardial contraction led the authors to study the effect of induced lipæmia in humans with known severe coronary artery disease and angina pectoris. Fourteen such patients were given a fatty meal containing 0.6 g. butterfat per pound body weight to induce lipæmia. Patients were resting during the test, smoking was not allowed and electrocardiograms, ballistocardiograms and blood samples were taken before and at suitable intervals after the test meal. By giving a fat meal small in volume and slow in rate of absorption from the gastrointestinal tract, the early deleterious effect of a meal on the circulation of these patients was minimized. Peak lipæmia was observed five hours after the test meal. A total of 14 typical attacks of angina was precipitated in six of the 14 patients. Each of these attacks occurred when plasma lactescence was at or near peak value. Definite transient changes were noted in the electrocardiograms of four of these patients. These changes included an increase in heart rate, an increased depression of the RS-T segment, a change in the amplitude of the T waves, and the appearance of ventricular extrasystoles. In six patients marked changes in the ballistocardiogram were observed during each of the 14 attacks of angina. For purposes of control a meal low in fat but of the same bulk and caloric content as the fat meal was given to three of the patients who had previously shown a positive response to the fat meal. No anginal pain was elicited in any of these patients. The possibility that slowly rising and prolonged lipæmia may be considered one of the factors responsible for the production of the syndrome of anginal decubitus was considered. A low fat diet might be useful in the management of patients with angina pectoris as a measure to help prevent pain.

N. W. MCQUAY

Hemoptysis, Bronchial Erosion and Bronchitis.

ANDERSON, A. E., JR., BUECHNER, H. A. AND ZISKIND, M. M.: ANN. INT. MED., 42: 1246, 1955.

In approximately one-fourth of all cases of hæmoptysis no cause is found for this symptom, even after exhaustive diagnostic studies have been carried out. Frequently such patients quickly recover their usual state of health and have no further difficulty. In such cases, it appears obvious that these individuals do not have cancer or tuberculosis or even bronchiectasis, and the hæmoptysis must be attributed to a much less serious disorder. The purpose of this paper is to suggest that a hæmoptysis may result from erosive lesions of the bronchi, with particular reference to relatively minor inflammatory disease, such as bronchitis, as a cause.

Bronchial erosion may be said to be a result of coughing and cyclic bronchial action on an area of lowered tissue resistance produced by a variety of pathological states. Five cases are reported in which hæmoptysis occurred, and no satisfactory explanation could be found with the exception of simple bronchial erosion produced by bronchitis. In all cases, bronchoscopic examination was done, and mucosal biopsy, at or near a suspicious site, revealed ulceration and intense submucosal inflammatory reaction.

Treatment consisted primarily of rest in bed, gentle suppression of the cough reflex, and antibiotics. No local applications were made to these simple erosions of the bronchial mucosa. In all cases, complete recovery took place, and repeated examinations revealed no evidence of persistent disease.

The authors feel that many, and perhaps most, cases of so-called idiopathic hæmoptysis may be explained on the basis of minor inflammatory changes of the bronchi which produce erosion of the mucosa in areas that may or may not be accessible to the bronchoscope.

S. J. SHANE

Observations on Distension of the Lower End of the Œsophagus.

BAYLIS, J. H., KAUNTZE, R. AND TROUNCE, J. R.: QUART. J. MED., 24: 143, 1955.

The present study was carried out to assess the differential diagnostic problem between œsophageal and cardiac pain. A balloon was inflated in the lower œsophagus in eight normal subjects and in three with coronary artery disease and the results were carefully studied clinically and by radiography and electrocardiography. The induced œsophageal pain differed from the pain of cardiac ischæmia in many respects, and no effect was induced electrocardiographically even in the cardiac patients. Atropine was found to have no analgesic effect upon the pain whereas amyl nitrite abolished it through temporary inhibition of œsophageal contraction induced by the distension.

The authors are of the opinion that the electrocardiogram offers the most reliable means of distinguishing between œsophageal and cardiac pain.

NORMAN S. SKINNER

Treatment of Cardiac Arrest and Slow Ventricular Rates in Complete A-V Heart Block. Use of Molar and Half Molar Sodium Lactate.

BELLET, S., WASSERMAN, F. AND BRODY, J. I.: CIRCULATION, 11: 685, 1955.

There are few dependable drugs available for increasing the ventricular rate in complete A-V block during prolonged sinus pauses and following cardiac arrest occurring in association with anæsthesia and other states. These drugs include epinephrine, Isuprel, atropine, Banthine, Paredrine and others.

The authors report the effects of sodium lactate (molar and half molar) solutions: (a) in restoring ventricular beating during repeated episodes of cardiac standstill of Stokes-Adams seizures; (b) during episodes of cardiac arrest of other etiologies; (c) in increasing the ventricular rates in states accompanied by slow heart rates, e.g. varying grades of partial A-V heart block and sinus bradycardia; and (d) in increasing the rate of ventricular beating in complete A-V heart block.

They employed a dose ranging from 15 c.c. of molar sodium lactate administered in about one minute to a total of 960 c.c. (molar and half molar solution) administered within a period of five hours. The rapidity of injection depended upon the urgency of restoring the heart rate.

In all cases studied, the desired effect was produced; the writers conclude that sodium lactate appears to increase cardiac rhythmicity while possessing little or no pressor action. No dangerous ectopic rhythms were produced.

These observations suggest that molar and half molar sodium lactate solutions possess qualities that should be of help in the prevention and treatment of sudden cardiac standstill.

S. J. SHANE

SURGERY

The Primary Repair of Wounds of Major Arteries.

HUGHES, C. W.: ANN. SURG., 141: 297, 1955.

The author outlines in this article, in detail, 72 major arterial repairs which he performed as a member of the Surgical Research Team in Korea, and refers to other comparable series studied in Korea. A total of 130 major vessel injuries were repaired, followed up, and reported by three members of the Surgical Research Team. The amputation rate for these was 11%, as compared to 36% for a comparable series in World War II. The results of members of this team were noticeably better than those obtained by other surgeons in Korea, not as well trained in this particular surgical field; hence the need for special cardiovascular centres.

Reference is made to the present techniques and various factors responsible for the superior results in Korea. The small percentage which could be repaired by lateral suture produced the lowest incidence of amputation and other complications. Most of the repairs (65%) were accomplished by direct anastomosis and this produced the next most satisfactory results. Autogenous vein graft and homologous arterial graft, although often very useful and in some cases the only alternative, resulted in a higher incidence of thrombosis.

Interesting observations include the questionable value of sympathectomy for the acute traumatic vascular lesion. Some patients were found by different observers to have good blood flow through necrotic muscle at the time of amputation, the muscle having undergone irreversible changes prior to reconstruction of the artery. Numerous patients were seen in whom the injured limb was cold, ischæmic, anæsthetic and paralytic with fixed joints. After repair, warmth would return, and superficially for a short interval at least, results would seem to have been good. However, later œdema would increase and at time of fasciotomy necrotic muscle would often become obvious. Hæmorrhage from the suture line or infection at the site of the repair was uncommon.

Many factors enter into the final results of arterial repair but of these time lapse is undoubtedly of the greatest importance.

ALLAN DAVIDSON

Management of Arterial Injuries in Battle Casualties.

SPENCER, F. C. AND GREIVE, R. V.: ANN. SURG., 141: 304, 1955.

This report presents 97 arterial injuries in 85 patients treated while the authors were on active military duty with the First Marine Division in Korea. Arterial repair was considered for all major arterial injuries. No extremities were seen in which ischæmic changes were so marked that a primary amputation was done.

Small wounds with no active bleeding but associated with a history of shock at the time of injury were often found to have an arterial injury sealed by a blood clot. Others have indicated that 50% of vascular wounds are not found until the time of debridement.

All grossly injured arterial tissue was removed, but the extensive dissection described by Janke and Seeley was

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not done. Rather than take the chance of jeopardizing collateral vessels in order to mobilize the adjacent segments to carry out direct anastomosis, these workers favoured the use of arterial homografts. Most grafts were 4 to 6 cm. in length—a few 9 to 12 cm. These were obtained "in the field" by autopsy under sterile conditions and stored in a blood bank refrigerator at between 0° and 10° C. for a maximum of six weeks. Following debridement, the soft tissues were approximated by sutures around the repair site to surround the artery with a viable soft tissue bed. Consistent with the general principle in military surgery, the remainder of the wound was left open for closure by delayed primary suture.

It was considered imperative to immobilize in a posterior plaster splint for three weeks. Adequate blood replacement was felt to be the most important factor in preventing peripheral vasoconstriction. The time interval between injury and arterial repair was considered the most important factor by these as well as other authors. Also, arterial injuries associated with compound fractures have a poor prognosis, with almost 100% failure of repair.

There is now a definite tendency to repair major venous injuries, contrary to the common practice in the last war. Gangrene in three cases seen with satisfactory arterial repair was attributed to massive venous occlusion.

In this series the over-all amputation rate was 22%, being 5% for brachial, 21% for femoral and 38% for popliteal artery injury.

Back-bleeding was not found to be an infallible criterion of whether an extremity would survive after arterial ligation. "Good" or "fair" was the description of back-bleeding present in nine of 20 extremities that subsequently became gangrenous. ALLAN DAVIDSON

OTORHINOLARYNGOLOGY

Harmful Sequelæ of Adenoidectomy in Children with Chronic Sinusitis.

BROWN, E. E.: ARCH. PEDIAT., 71: 233, 1954.

Occlusion of the nasopharynx by adenoid tissue, a rare condition, is the main indication for adenoidectomy. Mouth-breathing is due to nasal infection or obstruction, seldom to the adenoids; adenoidal compression of the Eustachian tubes, sufficient to impair hearing, is unusual.

The adenoids rarely become infected, and chronic mucopurulent postnasal discharge comes from infected sinuses. Removal of the adenoids, which act as a barrier against infection of the lower respiratory tract, increases the incidence of laryngitis, bronchitis, bronchiectasis, bacterial asthma and pneumonia.

Most of the conditions usually attributed to the presence of adenoids (catarrh, mouth breathing, recurrent otitis media, mastoiditis, deafness) result from sinus infection, treatment of which is essential. I. J. PATTON

RADIOLOGY

The Demonstration of Left Atrial Enlargement by Body Section Radiography.

PASTOR, B. H., WOHL, G. T. AND LAWRENCE, L. T.: CIRCULATION, 11: 400, 1955.

Although the signs of left atrial enlargement are well known, they are sometimes difficult to demonstrate in conventional roentgenograms. The authors have found body section radiography (planigraphy) helpful in delineating enlarged left atria in patients in whom the enlargement was not satisfactorily defined by the standard roentgenological method of heart study.

Three specific features of this type of study recommend it to the writers: (1) In body section films, even without barium swallow, the border of the enlarged left atrium can be seen despite the obscuring shadow of the spine and independent of the position of the œsophagus. (2) In conventional roentgenograms the left atrial border is often ill defined, concealed by the right atrial border, or obscured by hilar shadows. Body section films in the frontal projection at appropriate levels clearly delineate the left atrial border from other structures with which it may be confused. (3) Gross enlargement of the left atrium usually takes place in an upward direction, widening the bronchial angle from the normal of about 70° to as much as 100° or more, and sometimes compressing both bronchi. This can occasionally be seen in conventional films, but is often not well visualized. The position of the bronchi can readily be demonstrated by body section films in the frontal projection at an appropriate level.

Reproductions of appropriate planigraphic views are included. S. J. SHANE

DERMATOLOGY

Lichen Planus.

TOMPKINS, J. K.: A. M. A. ARCH. DERMAT., 71: 515, 1955.

Follow-up studies were done on 41 patients who had lichen planus. No significant correlation with type of occupation could be made. Twenty-nine patients had extensive involvement; 12 had involvement of only one or two regions. This latter figure includes six patients who had oral mucous membrane lesions only. The generalized eruptions lasted from two months to two years, the localized eruptions from two to 20 years. The pruritus was more severe in the localized forms. A positive history of some precipitating factor of an emotional nature was obtained in 20 of the 41 patients. It was noted that in patients with the hypertrophic variety there was a continual healing of old lesions and formation of new ones. Apart from the symptomatic relief of itching, the treatment of lichen planus did not influence the course of the disease. Five of the 41 had recurrences.

The author comments that the emotional factors elicited might be only the trigger mechanism which sets off a disease which could have an underlying somatic cause. He also has the impression that the generalized form runs a more acute course with the rapid spread of lesions, but carries a better prognosis because it is of shorter duration.

[Widespread lymphadenopathy, which is not infrequently seen in cases of extensive lichen planus, is not mentioned in the article.] ROBERT JACKSON

PATHOLOGY

Effect of Oxygen on Developing Retinal Vessels with Particular Reference to the Problem of Retrolental Fibroplasia.

ASHTON, N., WARD, B. AND SERPELL, G.: BRIT. J. OPHTH., 38: 397, 1954.

The authors report on the experimental effects of high oxygen concentrations at atmospheric pressure on retinal vessels of kittens. They produced a type of vasoconstriction progressing to complete obliteration of the growing retinal vessel. This phenomenon is apparently confined to the developing retina. The severity of the vaso-obliteration is inversely proportional to the maturation of the vessels, and obliteration cannot be produced once the retinal vessels are fully mature; it is directly related to the duration of exposure and concentration of oxygen, concentrations below 35% having little or no effect in the most sensitive age groups. On transfer to air the obliterated vessels only partially reopen, producing hæmorrhages; the vascular closure is rendered permanent by thrombosis or adherence of the opposing endothelial cells through plasma coagulation. Profuse

vasoproliferation develops because this partially reopened network is inadequate to nourish the retina; if the obliteration has been total the retina is revascularized from the disc by a dense circular mass of vessels which extends into the retina in a profuse and disordered manner. Eventually the whole retina is revascularized, and arteries and veins differentiate, with the intravitreal vessels gradually disappearing in a postero-anterior direction. Normal histology is restored and vision is retained. Where obliteration has affected only the periphery of the retina, vasoproliferation and intravitreal growth are similarly confined to this region, a picture which exactly parallels that seen in most cases of stage-one retrolental fibroplasia. Obliterated vessels remained closed provided that the animal was kept in high concentrations of oxygen and that no pulmonary complications ensued; there was no difference in the degree of vasoproliferation on transferring the animals to reduced oxygen concentration rather than to air. Carbon dioxide up to 5% had no effect on either the vaso-obliterative or vasoproliferative phases, and Priscol did not appear to modify the vaso-obliterative phase in a single experiment. Anticoagulants profoundly modified the degree of vaso-obliteration. Return to a high concentration of oxygen to some extent controlled the secondary vasoproliferation, but the inevitable return to air was accompanied by an exacerbation of the process. The pathological vascular change, which begins in the first few hours of hyperoxia, is directly or indirectly due to the oxygen-enriched atmosphere. The literature contains numerous reports that increased oxygen causes vasoconstriction in the central nervous system of man and animals, but it would seem unlikely that the peculiar effect of oxygen on growing retinal vessels could be related to the known vasoconstrictor action of oxygen, because: (1) such vasoconstriction does not progress to vaso-obliteration; (2) such vasoconstriction is preventable by carbon dioxide, which had no effect in these experiments in concentrations up to 5%. It is not possible to explain vaso-obliteration solely by the action of oxygen on enzymes or by the unknown toxic effects postulated to account for the acute convulsive type of oxygen poisoning. The peculiar vulnerability of the growing vessels might be related to the unique anatomical and developmental relationships of the retinal and choroidal vessels; choroidal circulation maintains retinal nutrition during the early stages of development. As the choroidal supply becomes inadequate new retinal vessels bud into it. Raising oxygen tension in choroidal blood leads to increased oxygenation of the retina and, therefore, of the tissue into which the retinal vessels are budding; vaso-obliteration could be explained by postulating that the vasoformative stimulus is thus removed, further vascular growth ceases, the circulation slows down and vascular atrophy ensues. There is, however, a possibility that hyperoxygenation of the retinal tissue produces a vasoconstricting metabolite which gradually accumulates until the retinal arterioles close in spasm.

As regards the vasoproliferative phase, there is much to indicate that tissue hypoxia, or a metabolite produced in such circumstances, is an important factor in the vascularizing process. Such a concept of a vasoformative factor may readily explain experimental findings, provided it is also postulated that the factor is removed or utilized as the vessels are attracted into the tissue. With regard to the vasoproliferative phase, they consider that the retina suffers an acute oxygen lack on transfer to air. Since the obliterated vessels are prevented by coagulation from reopening adequately, the vasoformative factor accumulates in the retina, and seeps into the vitreous. Large vessels then bud into the retina from the disc or from reopened vessels, advance wildly into the retina and burst into the vitreous.

In relation to human retrolental fibroplasia the authors point out that prophylaxis is by far the most hopeful line of attack, and an urgent plea is made for the control of oxygen therapy in the treatment of the premature baby.

W. F. T. TATLOW

FORTHCOMING MEETINGS

CANADA

CANADIAN ASSOCIATION OF OCCUPATIONAL THERAPY, 25th Annual Convention, Royal York Hotel, Toronto, Ontario. (Miss Joy Miles, C.A.O.T., 331 Bloor Street West, Toronto 5.) October 29-31, 1955.

MONTREAL MEDICO-CHIRURGICAL SOCIETY, 23rd Annual Fall Clinical Convention, Montreal, Quebec. (Mrs. Gerda E. Copp, Executive Secretary, Suite 718, 1538 Sherbrooke St. West, Montreal 25.) October 31-November 5, 1955.

CANADIAN PUBLIC HEALTH ASSOCIATION, Laboratory Section, Annual Christmas Meeting, Royal York Hotel, Toronto, Ontario. (Dr. F. O. Wishart, Secretary, Laboratory Section, C.P.H.A., 150 College St., Toronto 5.) December 12-13, 1955.

CANADIAN ASSOCIATION OF RADIOLOGISTS—19th annual meeting, Hotel Vancouver, Vancouver, B.C. (Dr. H. Brooke, Hycroft Medical Building, Granville St. at 16th Ave., Vancouver, B.C.) January 16-18, 1956.

SOCIETY OF OBSTETRICIANS AND GYNÆCOLOGISTS OF CANADA—1956 Annual Meeting, Manoir Richelieu, Murray Bay, Quebec. (Dr. F. P. McInnis, Secretary, Society of Obstetricians and Gynæcologists of Canada, 1230 Avenue Road, Toronto, Ont.) June 8-10, 1956.

CANADIAN MEDICAL ASSOCIATION, 89th Annual Meeting, Ecole de Commerce, Quebec, Quebec. (Dr. A. D. Kelly, General Secretary, Canadian Medical Association, 244 St. George Street, Toronto 5, Ont.) June 11-15, 1956.

UNITED STATES

AMERICAN HEART ASSOCIATION, Annual Meeting and Twenty-Eighth Annual Scientific Session, Jung Hotel, New Orleans, Louisiana. (The Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N.Y.) October 22-26, 1955.

INTER-SOCIETY CYTOLOGY COUNCIL, 3rd Annual Meeting, Statler Hotel, Cleveland, Ohio. (Dr. P. F. Fletcher, Secretary-Treasurer, 634 N. Grand Blvd., St. Louis 3, Mo.) November 11-12, 1955.

AMERICAN PUBLIC HEALTH ASSOCIATION, INC., 83rd Annual Meeting and Meetings of Related Organizations, Kansas City, Missouri. (The American Public Health Association, Inc., 1790 Broadway, New York 19, N.Y.) November 14-18, 1955.

NATIONAL SOCIETY FOR CRIPPLED CHILDREN AND ADULTS, Annual Convention, Palmer House, Chicago, Illinois. (Director of Information, 11 South LaSalle Street, Chicago 3.) November 28-30, 1955.

NEW YORK HEART ASSOCIATION, Conference on Rheumatic Fever and Heart Disease, Biltmore Hotel, New York, N.Y. (New York Heart Association, 485 Fifth Avenue, New York 17.) November 29, 1955.

AMERICAN MEDICAL ASSOCIATION, Clinical Meeting, Boston, Massachusetts. (Dr. George F. Lull, 535 North Dearborn Street, Chicago 10, Illinois.) November 29-December 2, 1955.

AMERICAN PSYCHOSOMATIC SOCIETY, 13th Annual Meeting, Sheraton-Plaza Hotel, Boston, Massachusetts. (Dr. S. Cobb, Chairman, Programme Committee, 551 Madison Avenue, New York 22, N.Y.) March 24-25, 1956.

INTERNATIONAL ANÆSTHESIA RESEARCH SOCIETY CONGRESS, Flamingo Hotel, Miami Beach, Florida. (Dr. T. H. Seldon, Mayo Clinic, Section on Anæsthesiology, Rochester, Minn.) April 9-12, 1956.

WORLD CONFEDERATION FOR PHYSICAL THERAPY, Second International Congress, New York, N.Y. (Miss M. J. Neilson, Secretary-General, c/o Chartered Society of Physiotherapy, Tavistock House South, Tavistock Square, London, W.C.1, England.) June 17-23, 1956.

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OTHER COUNTRIES

ASSOCIATION OF ANÆSTHETISTS OF GREAT BRITAIN AND IRELAND—Annual Meeting, London, England. (Association of Anæsthetists of Great Britain and Ireland, 45 Lincoln's Inn Fields, London, W.C.2.) November 3, 1955.

PHYSIOLOGICAL SOCIETY — Meeting, London, England. (Professor A. A. Harper, Dept. of Physiology, King's College, Newcastle-upon-Tyne, England.) November 4-5, 1955.

SOCIETY OF THORACIC SURGEONS OF GREAT BRITAIN AND IRELAND, Glasgow, Scotland. (Mr. J. Leigh Collis, F.R.C.S., 15 Highfield Road, Edgbaston, Birmingham, England.) November 4-5, 1955.

INTERNATIONAL CONGRESS OF ALLERGOLOGY, Rio de Janeiro, Argentina. (Dr. F. W. Wittich, 424 LaSalle Medical Bldg., Minneapolis, Minn.) November 6-12, 1955.

GENERAL MEDICAL CONGRESS, Faculty of Medical Sciences, Rosario, Argentina. (Dr. Adrian Menossi, Congreso General de Medecina, Facultad de Ciencias Medicas, Calle Santa Fe 3100, Rosario.) November 7-12, 1955.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION—quarterly meeting, London, England. (The Secretary, R.M.P.A., 11 Chandos St., Cavendish Square, London, W.1.) November 9-10, 1955.

SOCIETE D'OPHTHALMOLOGIE DE FRANCE, Bordeaux, France. (Dr. E. Bessiére, 9 rue Hustin, Bordeaux.) November 12-13, 1955.

BRITISH TUBERCULOSIS ASSOCIATION, Manson House, 26 Portland Place, London W.1, England. (The Secretary, B.T.A., 59 Portland Place, London, W.1.) November 18, 1955.

SIXTH VENEZUELAN CONGRESS OF MEDICAL SCIENCES, Caracas, Venezuela. (Dr. A. L. Briceno Rossi, Apartado 4412, Ofic. del Este, Caracas, Venezuela.) November 18-26, 1955.

BRITISH ASSOCIATION OF SPORT AND MEDICINE—Meeting, St. Thomas's Hospital, S.E.1, London, England. (Dr. D. J. Cussen, British Association of Sport and Medicine, 95 Mount Street, London, W.1.) November 21, 1955.

BRITISH ASSOCIATION OF PLASTIC SURGEONS, Annual Meeting, London, England. (British Association of Plastic Surgeons, 45 Lincoln's Inn Fields, London, W.C.2.) December 9-10, 1955.

PHYSIOLOGICAL SOCIETY—Meeting, London, England. (Professor A. A. Harper, Department of Physiology, King's College, Newcastle-upon-Tyne 1, England.) December 16-17, 1955.

INTERNATIONAL CONGRESS FOR THE SOCIAL REHABILITATION OF THE LEPER, Rome, Italy. (M. F. Sarsale, International Congress for the Rehabilitation of the Leper, Via Condotti, Palazzo Malta, Rome.) April 16-18, 1956.

INTERNATIONAL UNION FOR PUBLIC HEALTH EDUCATION, Third Conference, Rome, Italy. (M. Lucien Viborel, Secretary-General, 92 rue St. Denis, Paris Ier, France.) April 27-May 5, 1956.

INTERNATIONAL FERTILITY ASSOCIATION, SECOND WORLD CONGRESS, Naples, Italy. (Prof. G. Tesauro, President of Committee Arrangements, S. Andrea delle Dame, 19, Naples.) May 1956.

NINTH WORLD HEALTH ASSEMBLY, Geneva, Switzerland. (World Health Organization, Palais des Nations, Geneva.) May 9, 1956.

INTERNATIONAL MEDICO-ATHLETIC FEDERATION, 11th Congress, Buergenstock, Switzerland. (Dr. G. Schoenholzer, Secretary-General, Bluemlisalpstr. 7, Muri-Berne, Switzerland.) May 29-June 1, 1956.

BOOK REVIEWS

NEUROLOGY

S. A. Kinnier Wilson, Senior Neurologist, King's College Hospital. 2nd ed. Vols. I, II and III. 2,212 pp. Illust. Butterworth & Co. Ltd., London; Butterworth & Co. Ltd., Toronto, 1954.

This work, the distillate of a long career in neurology by a most incisive and encyclopædic mind, constitutes a veritable library of neurology. It was first published in 1940, three years after Kinnier Wilson's premature death, by Dr. A. Ninian Bruce. He has now brought us a second edition, with important additions—on aphasia, apraxia and agnosia by Sir Russell Brain, and on neurosyphilis by the distinguished British neuropathologist Dr. Samuel Nevin.

The three volumes are a treasure house of beautifully stated clinical descriptions, with discussions of etiology and treatment. No one need read a volume on the history of neurology after reading Kinnier Wilson. For him the subject flows uninterruptedly from the earliest descriptions to his own acute summaries of the broad picture.

It is a pleasure to read about the intricacies of the nervous system without forever wondering what the author really means. The clarity of expression seen in Kinnier Wilson's original contribution on hepatolenticular degeneration is carried on in these three volumes. Equally clear are his simple, unequivocal illustrations.

Some may quibble that the use of the latest antibiotic is not given as much prominence here as it evidently merits in the advertising fare to which we are prey today. It is simply a matter of perspective, and these volumes, with their superb bibliographic references to the earlier works in neurology, form a great counterweight to the glib accounts of neurological "cure" today in a series involving "one unselected case."

The 112 chapters range from the toxi-infective diseases of the nervous system to the degenerative, vascular and metabolic ones. In a period of increasing interest in the diseases of an aging population, Kinnier Wilson's exhaustive descriptions should be at the hand of all neurologists and neuropathologists.

The range of Wilson's reading and personal contributions in neurology is evident throughout the text. One moment he will be quoting Harold Dew in Australia and the next Herbert Olivecrona in Stockholm. Born in New Jersey, educated in Edinburgh and Paris, the great teacher at Queen Square was truly a part of all that he had seen. His three volumes have condensed this vast experience for the modern reader in an unprecedented fashion. Important contributions to neurology of the last few years have been incorporated into the study by the editor.

HANDBUCH DER ALLGEMEINEN PATHOLOGIE

(Handbook of General Pathology.) Vol. 6, Part I.

Edited by F. Büchner. 542 pp. Illust. 122.50 Marks. Springer-Publishers, Berlin, Göttingen, Heidelberg, 1955.

One hundred years ago R. Virchow published the now classical *Handbook of General Pathology*. In 1908 Krehl and Marchand started on a new handbook of general pathology which remained unfinished, the last volume having appeared in 1924.

With the progress which natural sciences and medicine have accomplished since that time, Büchner, Letterer and Roulet felt the need for a new compilation. The goal of these editors is the correlation of anatomical and functional disorders with their morphological, histological, cytological, biochemical and physical changes.

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The whole work will comprise twelve volumes, most of them divided into two parts.

In the section on general teratology (by A. Werthemann, Basel), the causal agents of malformations in the human embryo are studied in some detail; oxygen deficiency, virus infections, food deficiencies, damages due to x-ray and gamma radiation, and placental abnormalities are discussed. The next three chapters on the biology of growth deal with cell multiplication, growth of organs, body growth, hypertrophy, and hyperplasia, the development of giant cells and metaplasia. This interesting part is completed by a discussion on the biochemistry of cell multiplication and differentiation. The final part of this volume is devoted to the problem of regeneration and is subdivided into chapters on regeneration in plants and in animals and the process of physiological regeneration in man.

An extensive bibliography is found at the end of each of the main chapters. A complete index of authors and sujects completes the volume. Print and illustrations are excellent.

This volume will be of great interest to all German-reading physicians and biologists.

COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION.

Edited by R. M. Hewitt, A. B. Nevling, J. H. Miner, J. R. Eckman, M. K. Smith, C. M. Gambill, F. Schmidt and G. G. Stilwell. Vol. XLVI. 843 pp. Illust. W. B. Saunders Company, Philadelphia and London, 1955.

This is the 46th volume in the series of *Collected Papers of the Mayo Clinic* and, in the main, is based on activities there in 1954.

Compilation of these annual publications is affected by the projected size of the book, the merit of the contribution and the interest of the potential purchasers. Decisions have, at times, to be made somewhat arbitrarily and the editors of this volume are to be commended for the impartiality and general good sense which they have brought to their task. Although the size of the book naturally precludes any encyclopædic approach, there is, nevertheless, a satisfying variety and range in what is included. The general practitioner will find much to give him guidance and every specialist will come upon something helpful to him no matter how narrow his field. Of the omissions the most notable, perhaps, are the arthritides, the province in which the Clinic has attained such an outstanding position by its additions to our laboratory and clinical knowledge. No reason for these omissions is given.

To make the contents more readily accessible they have been grouped into 12 sections which are subdivided or arranged by the title of the paper or by the subject. Some of these subdivisions are clinical studies, some are summations of therapy and some are expressions of the personal views or experience of the clinician. The clinical studies are especially impressive because the number of cases is always so large that the conclusions drawn from them rest on a foundation not easily shaken.

Any attempt to set forth the contributions in order of relative merit would almost certainly reflect some of the reviewer's prejudices. Physicians familiar with the history of the Mayo Clinic will probably turn promptly to the section on the alimentary canal and to that on the ductless glands to learn whether or not the Clinic still keeps its position as a leading authority in these fields. Choice among the other sections will be a matter of taste or interest rather than a judicial appraisal of the intrinsic worth of the section chosen.

Readers of former volumes of the *Collected Papers* will need only to study the table of contents to gauge the appeal to them of this 46th volume. To those not yet acquainted with the writing style of the Mayo Clinic group the assurance can be given with confidence that the prevailing tone is sanity. There is no chasing obstinately after alluring gleams and no tendency to rest complacently on an established reputation.

WORLD HEALTH ORGANIZATION TECHNICAL REPORT SERIES NO. 93: EXPERT COMMITTEE ON MIDWIFERY TRAINING

First Report. 21 pp. World Health Organization, Palais des Nations, Geneva, 1955.

The subject considered in this report is not of direct interest to Canada, but is of vital importance to many governments of underdeveloped countries, in which there is an acute shortage of physicians and trained obstetric attendants. It is these areas which will benefit from this report, in which Miss Lyle Creelman, formerly of Vancouver and now Chief of the Nursing Section of WHO, has had a hand. The Expert Committee first discussed the types of midwifery personnel (apart from physicians) who give aid in childbearing. They then considered details of training midwives, auxiliary midwives and traditional birth attendants, emphasizing that simple training of the latter groups will be needed for a long time in many areas, and is a very difficult job.

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STRESS SITUATIONS

Edited by S. Liebman, Medical Director, North Shore Health Resort, Winnetka, Illinois. 144 pp. $3.00. J. B. Lippincott Company, Philadelphia and Montreal, 1955.

This is a small book, which contains a series of seven lectures by as many leading psychiatrists of the United States. Each of them discusses the emotional reactions of people to one of the stress-producing experiences of life. These stress situations are listed as frustration and failure, acute illness, catastrophe, marriage, divorce, fertility and sterility, death and suicide.

In the first essay on frustration and failure, it is emphasized that an emotion cannot exist alone, and that it may be expressed in many ways and even produce lesions. On this basis a doctor must recognize the existence of emotional needs of people and that he can help them, if only by letting them talk. Also, he can make suggestions for good mental hygiene if he understands people. However, the need is stressed for more research in the factors that maintain good mental health and predispose to mental ill-health.

The writers attempt to reason through and understand the reactions of people to these various ordeals. Some of the material is a little too didactic, though much of it is interesting to the general practitioner who wishes to learn what the psychiatrist is uncovering in these fields. There is considerable new and interesting knowledge—at least to this reviewer—particularly in the chapters on "Fertility and Sterility" and "Death and Suicide."

THE VISUAL FIELDS

A Study of the Applications of Quantitative Perimetry to the Anatomy and Pathology of the Visual Pathways.

B. Hughes, Professor of Neurosurgery in the University of Birmingham, Surgeon-in-Charge, Department of Neurosurgery, United Birmingham Hospitals, England. 174 pp. Illust. $9.75. Charles C Thomas, Springfield, Illinois; The Ryerson Press, Toronto, 1954.

It is always pleasant to find a medical textbook that presents a clear summary of an experienced clinician's major study. Professor Hughes is a neurosurgeon who is convinced of the great practical importance of visual perimetry in neurological diagnosis. The evidence of his own wide thinking and extensive experience is everywhere evident in his book. He emphasizes and proves the importance of principles that most clinicians have once learned, but come to neglect: the virtue of doing one's own perimetric studies, the practical value of quantitative perimetry. The report is divided into three parts: methods of perimetry, the anatomical principles involved, and the types of visual field defect encountered in different pathological states, such as compression, vascular diseases, and injury. The author develops a plan for examination that is not rigid but can be modified after an initial survey of the visual fields, in the light of the clinical picture. This will be a valuable addition to the working library of the neurologist, neurosurgeon and ophthalmologist.

PROSPECT AND RETROSPECT IN NEUROLOGY

Second Foundation Volume, published by the staff to commemorate the opening of the McConnell wing and the second foundation of the Montreal Neurological Institute, McGill University. 137 pp. Illust. $5.00. Little, Brown & Company, Boston 6, 1955.

This small volume is a compendium of lectures and addresses relating the story of an important occasion in Canadian medical history. It was published to commemorate the opening of the McConnell Wing of the Montreal Neurological Institute in November 1954, and tells about the second foundation of the Institute. It contains essays by Dr. Alan Gregg of the Rockefeller Foundation and Sir Geoffrey Jefferson, dean of British neurosurgeons, as well as by members of the staff of the Institute, past and present. There are also summaries of a few outstanding scientific reports given during the foundation ceremonies. Although the book was not intended as such, it is in essence a tribute to the personality and guiding genius of the retiring Director of the Institute, Dr. Wilder Penfield. This is recommended for medical historians, and for all of the large throng of neurological scientists who have enjoyed any contact, however fleeting, with the Montreal Neurological Institute.

TOMMY, THE TIPSY TABBY

Alcoholism Research Foundation. Available on request. Toronto 5, Ont., 1955.

The Alcoholism Research Foundation, 9 Bedford Road, Toronto, has produced an amusing strip cartoon entitled "Tommy, the Tipsy Tabby", describing some of Masserman's experiments on cats and alcohol. It is well drawn and well written, and should be useful as a painless method of imparting basic facts about alcohol and alcoholism to the fairly intelligent layman.

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MEDICAL STUDENTS AND MEDICAL SCIENCES

D. C. Sinclair, University Demonstrator in Human Anatomy, Oxford University, England. 154 pp. $3.75. Oxford University Press, London and Toronto, 1955.

Factual comparisons between practices in medical education in America and the United Kingdom have not previously been as dispassionately made as in this concise volume, resulting from the author's visit to this continent in 1953. While he frankly admits that he has no answers to some of the questions on medical education which arise from his inquiry into pre-clinical educational procedures, two statements given in the preface are possibly the key to any fruitful discussion of his topic: "the first is that the study of medicine can be a worthy *education* for a man of capability and good sense"; and "the teaching of the medical sciences is an important and responsible job which, like any other job, has to be *learnt*" (the italics are the reviewer's).

The material is well arranged, presented with enthusiasm, scholarship and humour, and should be read by all those interested in undergraduate medical education—including medical students about whose studies it is written, and concerning whose "education" such extensive inquiry and experimentation in method and content is being conducted both in Europe and in America. Particularly noteworthy are the chapters on student selection, and on the teacher and teaching methods. The final chapter on current experiments in medical education gives a succinct account of activity in this field in the United States. This book is heartily recommended.